Stephen P. Swinton (SBN 106398)
Ashley N. Johndro (SBN 274807)
LATHAM & WATKINS LLP
12670 High Bluff Drive
San Diego, CA 92130
Telephone: (858) 523-5400
Facsimile: (858) 523-5450
Email: steve.swinton@lw.com
Email: ashley.johndro@lw.com

Nina M. Gussack
Kenneth J. King
PEPPER HAMILTON LLP
3000 Two Logan Square
Eighteenth & Arch Streets
Philadelphia, PA 19103-2799
Telephone: (215) 981-4000
Facsimile: (215) 981-4750
Email: gussackn@pepperlaw.com
Email: kingk@pepperlaw.com

Attorneys for Defendant
Eli Lilly and Company, a corporation

Richard B. Goetz (SBN 115666)
Amy J. Laurendeau (SBN 198321)
O'MELVENY & MYERS LLP
400 South Hope Street
Los Angeles, California 90071-2899
Telephone: (213) 430-6000
Facsimile: (213) 430-6407
Email: rgoetz@omm.com
Email: alaurendeau@omm.com

Attorneys for Defendant
Amylin Pharmaceuticals, LLC

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

IN RE INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

This Documents Relates to All Cases

CASE NO. 3:13-MD-02452-AJB-MDD

DECLARATION OF STEPHEN P. SWINTON IN SUPPORT OF DEFENDANTS AMYLIN PHARMACEUTICALS, LLC AND ELI LILLY AND COMPANY'S MOTION TO STRIKE FROM THE PUBLIC DOCKET OR, IN THE ALTERNATIVE, TO SEAL PLAINTIFFS' EXPERT REPORTS REGARDING PREEMPTION

Hon. Anthony J. Battaglia

I, STEPHEN P. SWINTON, declare as follows:

1. I am a partner in the law firm of Latham & Watkins LLP, and counsel of record for Eli Lilly and Company in the above-captioned matter. I have personal knowledge of the information set forth below and, if called as a witness, could and would testify competently thereto.

2. Attached hereto as Exhibit A is a true and correct copy of the expert report of David Madigan, redacted to seal the portions of the report that incorporate and reference Defendants' confidential documents.

3. Attached hereto as Exhibit B is a true and correct copy of the expert report of G. Alexander Fleming, redacted to seal the portions of the report that incorporate and reference Defendants' confidential documents.

I declare under the penalty of perjury of the laws of the United States that the foregoing is true and correct, and that this declaration was executed on January 6, 2015 in San Diego, California.

/s/ Stephen P. Swinton

EXHIBIT A

Incretins and Pancreatic Cancer

David Madigan, PhD

1. Credentials

1. I am Professor of Statistics at Columbia University in New York City where I am also the Executive Vice-President of Arts and Sciences and Dean of the Faculty. I was chair of the Columbia Department of Statistics from 2008 to 2013. I received my bachelor's degree in Mathematical Sciences from Trinity College Dublin in 1984 and was awarded the College's gold medal. In 1990, I received a Ph.D. in Statistics, also from Trinity College. I have worked in the past for KPMG, SkillSoft, University of Washington, AT&T Labs, and Soliloquy Inc. From 2005 to 2007 I was Professor of Statistics and Dean of Physical and Mathematical Sciences at Rutgers University. Prior to serving as Dean I was Director of the Rutgers University Institute of Biostatistics. I am an elected Fellow of both the Institute of Mathematical Statistics and the American Statistical Association, as well as the American Association for the Advancement of Science, an elected member of the International Statistical Institute, and was the 36th most cited mathematician worldwide from 1995-2005. I was an Institute of Mathematical Statistics Medallion Lecturer in 2009. I served a term as the Editor of *Statistical Science* from 2008 to 2010, the highest impact journal in Statistics.

2. I have published more than 150 technical papers on Bayesian statistics, biostatistics, pharmacovigilance, statistical graphics, Monte Carlo methods, computer-assisted learning, information retrieval, and text mining. Within the last few years I have consulted for Boehringer-Ingelheim, Clarus Therapeutics, CSL Behring, Jarvik Heart, Novartis, Pfizer, Sanofi-Aventis, Takeda, and Wyeth on a variety of issues, many related to drug safety. I have considerable statistical experience with clinical trials including the design and analysis of pain studies at the University of Washington and the Fred Hutchinson Cancer Research Center, both in Seattle, and service as a statistical consultant to multiple internal and external clients, particularly while I was director of the Institute of Biostatistics at Rutgers University, and continuing with Jarvik Heart.

3. Drug safety is one of my significant research interests, with a focus on the development and application of statistical methods for pharmacovigilance. I have published my work in *Drug Safety*, *Pharmacoepidemiology and Drug Safety*, *Therapeutic Advances in Drug Safety*, *Epidemiology*, the *American Journal of Epidemiology*, and other journals. I have also served as an investigator in the Mini-Sentinel project. Mini-Sentinel is a pilot project sponsored by the FDA to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. In 2010-11, I led the Mini-Sentinel Working Group on case-based methods in active surveillance. In addition, from 2010 to 2013 I was a Principal Investigator for the Observational Medical Outcomes Partnership (OMOP), a public-private partnership between the FDA and the pharmaceutical industry. The partnership conducted a multi-year initiative to research methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market. The OMOP work now continues in the Observational Health Data Sciences and Informatics collaborative where I

co-direct the Columbia-based coordinating center. I was a member of the FDA's Drug Safety and Risk Management Advisory Committee (DSaRM) from 2011 to 2014 and I continue to serve the FDA as a consultant. DSaRM advises the FDA Commissioner on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the FDA has regulatory responsibility. From 2010 to 2011 I was a member of a sub-committee of the FDA Science Board charged with reviewing the Center for Drug Evaluation and Research's pharmacovigilance program.

4. Further information concerning my background, training, and experience, including a complete list of my publications, is reflected in my curriculum vitae, a copy of which is attached as Appendix 2. A list of the testimony I have provided in the last four years is attached as Appendix 3.

2. Research Question

5. I was asked to examine whether a pancreatic cancer signal due to exposure to exenatide (Byetta, Bydureon), sitagliptin (Januvia, Janumet), or liraglutide (Victoza) exists in industry standard pharmacovigilance data sources. I was also asked to assess the strength of that signal, if any, in comparison to the signal, if any, for such events in other antidiabetic agents.

6. The approach I have taken to the work would have been the same had one of the manufacturers of these drugs hired me to carry out the analyses. I am being compensated at the rate of $700 per hour for my work on this matter. As I continue to review the data (or review newly provided data) I reserve the right to supplement and refine my report. All the opinions I express herein I hold to a reasonable degree of scientific certainty.

3. Background

3.1 Scientific Backdrop

7. Insulin is released from beta cells located in the endocrine compartment of the pancreas when GLP-1 receptors on the beta cells are stimulated by a hormone called Glucagon Like Peptide-1 or GLP-1. These same receptors are abundantly expressed in the exocrine pancreas on both the acinar and duct epithelial cells. The incretin class of drugs act to overcome the natural breakdown of the GLP-1 hormone in order to produce chronic stimulation of beta cells and increase the amount of insulin released into the blood stream. Several experimental animal studies have demonstrated that prolonged stimulation of the exocrine pancreas by GLP-1 agonist such as exenatide and liraglutide and the DPP-4 inhibitor--sitagliptin can produce cell proliferation and potentially promote the conversion of premalignant lesions to malignancies. Perfetti et al. (2000) reported that GLP-1 therapy

stimulated pancreatic cell proliferation in rats.[1] Brubaker and Drucker (2004) also reported that GLP-1 agents stimulated cellular proliferation and inhibited programmed cell death.[2] A high-dose toxicology study of liraglutide in cynomolgus monkeys revealed a 65% increase in exocrine pancreatic tissue.[3] More recently, Gale (2013) and Gier at al. (2012) reported animal studies showing that GLP-1 agents stimulated cell division and abnormal cell growth in the pancreas.[4]

8. [redacted]

9. I note that a number of analyses of the FDA's spontaneous report database have already appeared.[7] Each of these analyses showed pronounced safety signals for GLP-1 agents and pancreatic cancer.

3.2 Post-Marketing Safety Assessment

3.2.1 Post-Marketing Safety Assessment: Background

10. Prior to regulatory authorization, pharmaceutical companies conduct clinical trials of increasing scope and complexity culminating in large-scale randomized, controlled

---

[1] Perfetti, R., Zhou, J. I. E., Doyle, M. E., & Egan, J. M. (2000). Glucagon-like peptide-1 induces cell proliferation and pancreatic-duodenum homeobox-1 expression and increases endocrine cell mass in the pancreas of old, glucose-intolerant rats. *Endocrinology*, 141(12), 4600-4605.

[2] Brubaker PL, Drucker DJ. (2004) Minireview: Glucagon-like peptides regulate cell proliferation and apoptosis in the pancreas, gut, and central nervous system. *Endocrinology* 145: 2653–2659.

[3] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001026/WC500050016.pdf

[4] Gale EAM. (2013) GLP-1 based agents and acute pancreatitis. *BMJ* 346: f1263. 15; Gier B, Matveyenko AV, Kirakossian D, Dawson D, Dry SM, et al. (2012) Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras(G12D) mouse model. *Diabetes* 61: 1250– 1262.

[5] AMYLN03048141

[6] LILLY02444252 at 255 and AMYLN00240832

[7] Elashoff, M., Matveyenko, A. V., Gier, B., Elashoff, R., & Butler, P. C. (2011). Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1–based therapies. *Gastroenterology*, 141(1), 150-156; Nauck, M. A., & Friedrich, N. (2013). Do GLP-1–Based Therapies Increase Cancer Risk?. Diabetes care, 36(Supplement 2), S245-S252; ISMP QuarterWatch 2012 Q3 (http://www.ismp.org/quarterwatch/pdfs/2012Q3.pdf)

trials. After regulatory authorization, surveillance schemes based on spontaneous reporting system (SRS) databases are one of the cornerstones for the detection and evaluation of drug hazards. Pharmaceutical companies, health authorities, and drug monitoring centers use SRS databases for global screening for signals of new adverse events or changes in the frequency, character, or severity of existing adverse events (AEs) after regulatory authorization for use in clinical practice. The precise details of each SRS differ in terms of size and scope, statutory reporting mandates, surveillance selectivity or intensity, and organizational structure. Prominent SRSs include the Adverse Event Reporting System (AERS) of the United States Food and Drug Administration (FDA)[8], the Yellow Card Scheme of the Medicines and Healthcare Products Regulatory Agency (MHRA)[9], and the international pharmacovigilance program of the World Health Organization (the WHO Uppsala Monitoring Center)[10]. These systems were created to provide early warnings of possible safety problems that would be difficult to detect during clinical drug development because of the power limitations, constricted range of demographics, exclusion of patients with extensive co-morbid illnesses and co-medications, and limited duration of follow-up, characteristic of clinical trials.

11. The first step in signal detection is the submission of case reports of suspected adverse drug reactions and/or adverse events (AEs, i.e. any medical event coincident with drug therapy regardless of an index of suspicion by the reporter) to pharmaceutical companies and health authorities by healthcare professionals and/or patients. Although legally required in some countries, there is *de facto* voluntary reporting for all but pharmaceutical manufacturers. This introduces differential reporting of AEs. The literature surveying the factors that might influence reporting behavior is extensive.[11]

12. These reports are thereafter classified according to standardized AE coding dictionaries. This standardization facilitates signal detection at the case level and reduces data

---

[8] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm

[9] http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/yellowcard/yellowcardscheme.htm

[10] http://www.who-umc.org/

[11] Belton KJ: Attitude survey of adverse drug-reaction reporting by health care professionals across the European Union. The European Pharmacovigilance Research Group. *European Journal of Clinical Pharmacology* (1997) **52**(6):423-427; Belton KJ, Lewis SC, Payne S, Rawlins MD, Wood SM: Attitudinal survey of adverse drug reaction reporting by medical practitioners in the United Kingdom. *British Journal of Clinical Pharmacology.39(3):223-6,* (1995) **39**(3):223-226; Cosentino M, Leoni O, Banfi F, Lecchini S, Frigo G: Attitudes to adverse drug reaction reporting by medical practitioners in a Northern Italian district. *Pharmacological Research* (1997) **35**(2):85-88; De Bruin ML, Van Puijenbroek EP, Egberts AC, Hoes AW, Leufkens HG: Non-sedating antihistamine drugs and cardiac arrhythmias -- biased risk estimates from spontaneous reporting systems? *British Journal of Clinical Pharmacology* (2002) **53**(4):370-374; Eland IA, Belton KJ, Van Grootheest AC *et al.*: Attitudinal survey of voluntary reporting of adverse drug reactions. *British Journal of Clinical Pharmacology.48(4):623-7,* (1999); Williams D, Feely J: Underreporting of adverse drug reactions: attitudes of Irish doctors. *Irish Journal of Medical Science.168(4):257-61,* (1999):Dec.

corruption (e.g. inaccurate coding of reported AEs) at the level of individual records that could compromise statistical approaches based on aggregate data.

13. Algorithmic methods have emerged as an approach to identify such patterns. Different algorithmic approaches in pharmacovigilance include disproportionality analyses, sequential probability ratio tests, correlation analyses, and multivariate regression. Most of the practical experience to date has been with so called disproportionality analyses. While the precise operational details of each disproportionality algorithm vary, they all calculate surrogate observed-to-expected ratios in which the reporting experience of each reported Drug-Event Combination (DEC) is compared to the background reporting experience across all other drugs using an independence model.[12] In the appropriate clinical context, DECs that stand out statistically against the background reporting experience warrant additional investigation.

14. SRS data have some inherent, well-documented limitations relying as they do on voluntary reporting. Underreporting[13] is a particular concern that has been well documented and furthermore, the data provide limited temporal information to inform analyses. Nonetheless, despite new efforts to build active surveillance systems harnessing newer data sources, SRS systems provide the primary data for day-to-day drug safety surveillance by regulators and manufacturers worldwide. I concur with the FDA guidance[14] on the appropriate use of SRS data: "Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other premarketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug."

---

[12] Bate A, Lindquist M, Edwards IR *et al.*: A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol* (1998) **54**(4):315-321; Egberts AC, Meyboom RH, Van Puijenbroek EP: Use of measures of disproportionality in pharmacovigilance: three Dutch examples. *Drug Safety* (2002) **25**(6):453-458; Evans SJ, Waller PC, Davis S: Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf* (2001) **10**(6):483-486; Fram D, Almenoff J, DuMouchel W: Empirical Bayesian data mining for discovering patterns in post-marketing drug safety. Ninth ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, 2003; Szarfman A, Machado SG, O'Neill RT: Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf* (2002) **25**(6):381-392.

[13] Hazell L, Shakir SA (2006) Under-reporting of adverse drug reactions: a systematic review. *Drug Safety* **29**:385–396

[14] www.fda.gov/ohrms/dockets/98fr/04d-0117-gdl0002.doc

15. SRS data have played a role in many drug withdrawal decisions. Appendix 1 lists some examples.

3.2.2 Post-Marketing Safety Assessment: Analytic Approaches

16. SRSs receive reports that comprise one or more drugs, one or more AEs, and possibly some basic demographic information (in addition to narrative and text data). Over time, SRS databases emerge that contain thousands or even millions of these reports. Notwithstanding the data limitations discussed above, SRS databases represent a primary data source for evaluating drug safety. SRS databases present some computational challenges. The MedDRA adverse event coding system includes over 19,000 distinct Preferred Terms (PTs). The number of licensed drugs is of the same order of magnitude. Thus SRS databases resemble spreadsheets with one row per report and around 30,000 columns. Table 1 below shows a conceptual representation of a typical entry.

Table 1: A conceptual representation of a typical entry in an SRS database

Age	*Sex*	*Drug 1*	*Drug 2*	*…*	*Drug 15000*	*AE 1*	*AE 2*	*…*	*AE 16000*
42	Male	No	Yes	…	No	Yes	No	…	Yes

17. Researchers have developed a number of algorithms that search SRS databases for "interesting" associations. Most such algorithms (e.g. multi-item gamma-Poisson shrinker [MGPS], proportional reporting ratios [PRR], reporting odds ratios [ROR], Bayesian confidence propagation neural network [BCPNN]) focus on 2 X 2 tables constructed from these data. Table 2 shows a typical (fictitious) table for a fictitious drug called Ganclex and a real adverse event, nausea.

Table 2: A fictitious 2 X 2 table constructed from an SRS database

	Nausea Yes	**Nausea No**	**Total**
Ganclex Yes	**20**	**100**	120
Ganclex No	**100**	**980**	1080
Total	120	1080	1200

18. The number 20 in the upper left cell means there are 20 reports in the database that include Ganclex and list nausea as an adverse event. There are 100 reports in the database that include Ganclex but do not list nausea as an adverse event and thus a total of 120 reports exist in the database that include Ganclex. The second row concerns reports in the database that do not include Ganclex. Some 100 of these reports list nausea as an adverse event while 980 of these reports do not list nausea. This particular database has a total of 1,200 reports. Real SRS databases are of course much larger.

19. The basic analysis task then is to rank order the tables and report some subset of the DECs as worthy of further investigation. Many measures of signal strength exist and their statistical properties for hypothesis testing vary. MGPS focuses on the "reporting ratio" (RR). The RR for the Ganclex – nausea combination above (20 in the example above) divided by the expected number of occurrences. Since nausea occurs in 10% of all reports (120/1200), the expected number of nausea reports on Ganclex is 12, i.e., 10% of 120. Thus the RR for this example is 20/12 or 1.67; this combination occurred about 67% more often than expected. Some analysts use 2 as a threshold for signal strength and hence would not further investigate a DEC at this level (I revisit the issue of thresholds in Section 4.2.3).

20. The widely-used MGPS algorithm statistically estimates the RR using a Bayesian approach. The estimator is called EBGM (empirical Bayes geometric mean) and it generally provides a more conservative (i.e. closer to one) estimate than the one I described above. However, once the number in the upper left cell (20 in the example above) exceeds about 10, the EBGM and the simple estimator described above are typically very close.

21. MGPS produces a Bayesian confidence interval along with the EBGM. The lower end of a 90% interval is commonly referred to as EB05. Because it is the lower end of the interval, EB05 is always closer to one than the EBGM and is thus even more conservative than EBGM. This level of conservativeness is especially appropriate when screening for previously unsuspected drug-outcome associations.

22. The Proportional Reporting Ratio (PRR) is another widely used measure of association. The PRR is the fraction of the reports of the drug of interest (Ganclex in the example above) that contain the adverse event of interest (nausea in the example above) divided by the fraction of reports that do not mention Ganclex that contain nausea. Thus, for the example above, the PRR is (20/120) / (100/1080) which is 1.8. The Reporting Odds Ratio (ROR) is an older metric that was in use in the 1990's. The ROR is the odds of reporting the event of interest in reports that mention the drug of interest divided by the odds of reporting the event of interest in reports that do not mention the drug of interest. Thus, for the example above, the ROR is (20/100) / (100/980) which is 1.96.

23. Both the FDA and the Medicines and Healthcare Products Regulatory Agency in the UK use the MGPS algorithm, and, as I understand, both focus primarily on the EB05 measure. The PRR measure is much simpler and is also widely used. However with small upper left cell counts, the PRR is unstable and can yield very large or very small values with little or no statistical meaning.

3.2.3 Post-Marketing Safety Assessment: Signaling Thresholds

24. In practice, signal detection algorithms are often used with "signal thresholds" that dictate whether or a given drug-outcome pair generates a signal when broadly screening SRS databases. For example, a commonly applied threshold for PRR is 2 with a minimum chi-square value of 4 and a minimum case count of 3.[15] For MGPS, Szarfman and her co-authors proposed using a threshold of 2 for the EB05 measure[16] although other authors have suggested that EB05 is intrinsically too conservative in the sense that it could result in delayed detection of relevant signals. A 2010 review article[17] identified a wide variety of thresholds in actual use.

3.2.4 Post-Marketing Safety Assessment: Signal Refinement

25. The methods I have just described represent standard approaches to signal detection in SRSs that are used by regulators and pharmaceutical companies worldwide. I note that such signal analyses are not meant to quantify the extent of a drug's increased risks. Once a signal is detected, a wide variety of approaches are used to carry out "signal refinement," a process designed to shed further light on the signal. One standard approach is to compare reporting rates of the drug in question with reporting rates for specific other drugs in the same class (using, for example, the PRR). This was the approach adopted when a signal was generated for Baycol (cerivastatin) and rhabdomyolysis. In that context, the scientific community focused on the reporting rate for rhabdomyolysis and Baycol as compared with other market-leading statins.[18]

26. I note that FDA routinely compares reporting rates of different drugs and differential reporting can and does provide a basis for safety assessment and communications about potential safety risks. See, for example, an FDA Office of Surveillance and Epidemiology Review[19] comparing proportional reporting ratios ("PRR") and relative reporting ratios from AERS for five gadolinium-based contrast agents and concluding that "[t]he analysis of disproportional reporting from the AERS data within the gadolinium product class, shows safety signals for Omniscan and Optimark. . . . Reports of nephrogenic system fibrosis (NSF) are more frequent than expected with these two contrast agent drugs, when compared to the other three." This was also the approach adopted when a signal was generated for Baycol (cerivastatin) and rhabdomyolysis. In that context, the scientific community focused on the reporting rate for rhabdomyolysis and Baycol as

---

[15] Evans, SJW, Waller, D, Davis, D. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiology and Drug Safety*, **10**,(2001) 483-486.

[16] Szarfman A, Machado SG, O'Neill RT: Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf* (2002) **25**(6):381-392.

[17] Deshpande, G., Gogolak, V., Weiss Smith, S. Data Mining in Drug Safety: Review of Published Threshold Criteria for Defining Signals of Disproportionate Reporting. *Pharmaceutical Medicine*. **24**(1):37-43, February 1, 2010.

[18] Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. *Curr Control Trials Cardiovasc Med*, **2**(5) 205-207.

[19] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM190850.pdf

compared with other market-leading statins.[20] See also, Szarfman *et al.* Atypical antipsychotics and pituitary tumors: A pharmacovigilance study. *Pharmacotherapy* 2006, 26(6) 748-758 at Table 1 (study by FDA officer which includes a comparison of reporting rates for different atypical antipsychotics). Although such analyses do not precisely quantify the extent of any increased risks for, or differential risk among, various products, they do provide insight into relative safety concerns and safety signals for such products. The FDA Guidance[21] states "Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication.

27. Duplicate reports can occur in SRS systems and a number of authors have described algorithms for detecting duplicates. In the analyses presented below I removed duplicates defined as reports having identical manufacturer and control codes.

28. The so-called "Weber effect" states that adverse event reporting tends to increase in the first two years after a new drug is on the market, peaks at the end of the second year, and then declines.[22] The original paper posited this effect based on an analysis of adverse event reports for seven NSAIDs. Recent work,[23] however, considered a much more extensive set of drugs, and showed no evidence for a Weber effect. Other studies outside the NSAID context have also found no evidence to support the Weber effect.[24]

29. In some of my publications[25] I have expressed concern about confounding bias introduced by the so-called "innocent bystander" effect. The basic problem is as follows. Suppose Drug A causes a particular adverse event and Drug B does not. Further suppose that Drug A is commonly co-prescribed with Drug B. Then any analysis of Drug B will tend to incorrectly show an association with the adverse event. Drug B is an "innocent bystander."

---

[20] Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. *Curr Control Trials Cardiovasc Med*, **2**(5) 205-207.

[21] www.fda.gov/OHRMS/DOCKETS/98fr/04d-0189-gdl0002.doc

[22] Weber JCP. Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. *Adv Inflamm Res*. 1984;6:1–7.

[23] Chhabra, P., Chen, X., & Weiss, S. R. (2013). Adverse Event Reporting Patterns of Newly Approved Drugs in the USA in 2006: An Analysis of FDA Adverse Event Reporting System Data. *Drug safety*, *36*(11), 1117-1123; Hoffman, K. B., Dimbil, M., Erdman, C. B., Tatonetti, N. P., & Overstreet, B. M. (2014). The Weber Effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): Analysis of Sixty-Two Drugs Approved from 2006 to 2010. *Drug Safety*, 1-12.

[24] McAdams MA, Governale LA, Swartz L, Hammad TA, Dal Pan GJ. Identifying patterns of adverse event reporting for four members of the angiotensin II receptor blockers class of drugs: revisiting the Weber effect. *Pharmacoepidemiol Drug Saf*. 2008;17(9):882–9; Hartnell NR, Wilson JP, Patel NC, Crismon ML. Adverse event reporting with selective serotonin-reuptake inhibitors. *Ann Pharmacother*. 2003;37(10):1387–91.

[25] Hauben, M., Madigan, D., Gerrits, C., and Meyboom, R. (2005). The role of data mining in pharmacovigilance. *Expert Opinion in Drug Safety*, **4**(5), 929-948.

Together with co-authors, I have developed statistical methods to account for this problem[26] and I provide corresponding logistic regression[27] results in Section 5.

4. Methods

30. To conduct my analyses, I used the programming language perl (for data preparation and analysis), the statistical software package R (version 3.1.0), and the QScan pharmacovigilance platform provided by DrugLogic Inc. (Reston, VA). The QScan software has been validated extensively. DrugLogic uses a very detailed validation process (originally setup by an FDA software auditor). DrugLogic's software development process is CFR 21 Part 11 compliant. Many peer-reviewed publications report results derived from QScan.

31. In what follows I focus primarily on EB05 values stratified by age, sex, and year of report.

32. To identify exenatide, sitagliptin, and liraglutide reports I searched for reports containing the following drug names:

Exenatide:

- byetta
- exenatide
- bydureon

Sitagliptin:

- januvia
- janumet
- sitagliptin

Liraglutide:

- victoza
- liraglutide

33. [redacted]

[26] Caster, O., Noren, G.N., Madigan, D., and Bate, A. (2010). Large-Scale Regression-Based Pattern Discovery: The Example of Screening the WHO Global Drug Safety Database. *Statistical Analysis and Data Mining,* **3**, 197-208.
[27] CCD regularized logistic regression, normal prior, prior variance = 0.1, covariates are age, sex, year of report, and all drugs that occur at least 10 times in AERS.
[28] AMYLN03058141 at 148

34. I used sulfonylureas, rosiglitazone, and metformin as diabetes drug controls in my analysis. Dr. Fleming confirmed these choices. If diabetes itself causes pancreatic cancer, then the effect should also be apparent with these other drugs. The specific drugs I searched for are:

- avandia
- rosiglitazone
- glucotrol
- amaryl
- diabeta
- euglucan
- glynase
- micronase
- cetohexamide
- arbutamide
- hlorpropamide
- lipizide
- liclazide
- libenclamide
- lyburide
- libornuride
- liquidone
- lisoxepide
- lyclopyramide
- limepiride
- olazamide
- olbutamide
- metformin
- glucophage

5. Results

35. Here I report my analysis of AERS using the EB05 metric. EB05 is more conservative[29] than EBGM, PRR or ROR and as such, any signal flagged by EB05 would certainly generate a signal using the other metrics. Figure 1 shows the EB05 values over time for the pancreatic cancer. I provide the underlying numerical results for EB05 and other metrics for each figure in an Excel spreadsheet.

[29] "conservative" in the sense that it produces estimates closer to one.

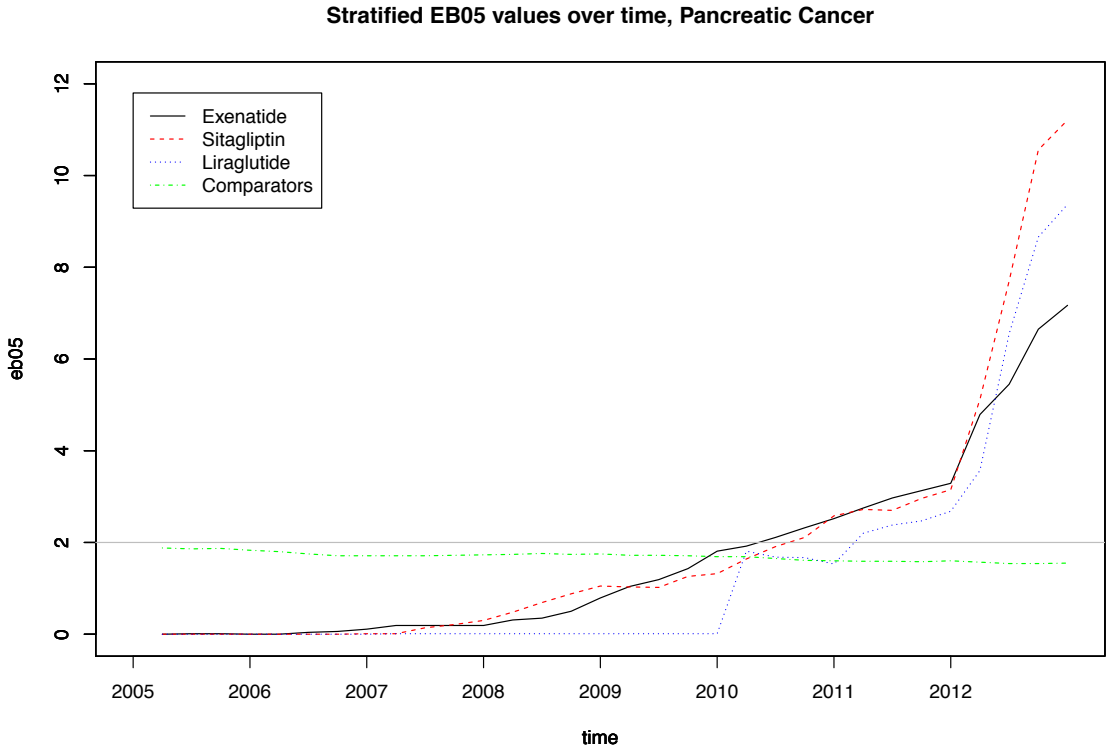


Figure 1. Stratified EB05 analysis for the pancreatic cancer for GLP-1 agents and the comparators.

36. Using the conventional threshold of 2, Figure 1 shows that the GLP-1 agents generated a signal for pancreatic cancer as early as 2010. The comparators never reach the signaling threshold.

37. Table 1 provides estimated effect sizes using regularized logistic regression. These are on the scale of odds ratios so that an estimate of one represents no effect while an estimate of, for example, 6.17 for Exenatide as of the end of 2012 represent a more than six fold increase in the odds of pancreatic cancer, adjusting for age, sex, year of report, *and all other drugs*. Using a threshold of 2, i.e. a doubling, all three GLP-1 agents show a safety signal as early as the end of 2010.

Table 1. Exponentiated regularized logistic regression coefficients for GP-1 agents and comparators for developmental delay. Logistic regression fit using the CCD software[30] with a prior variance of 0.1.

	Year Ending				
	2008	**2009**	**2010**	**2011**	**2012**
Exenatide	1.12	2.16	2.92	3.69	6.17
Sitagliptin	1.53	1.85	3.06	3.42	6.69
Liraglutide	n/a	n/a	2.08	4.03	7.51
Comparator	1.98	1.90	1.82	1.79	1.64

[30] https://github.com/OHDSI/CCD

38. I conducted a number of sensitivity analyses. Some authors restrict analyses of spontaneous reports to reports where the drug of interest is marked as "primary suspect," while others only consider "serious" reports. Figures 2 and 3 provide such analyses.

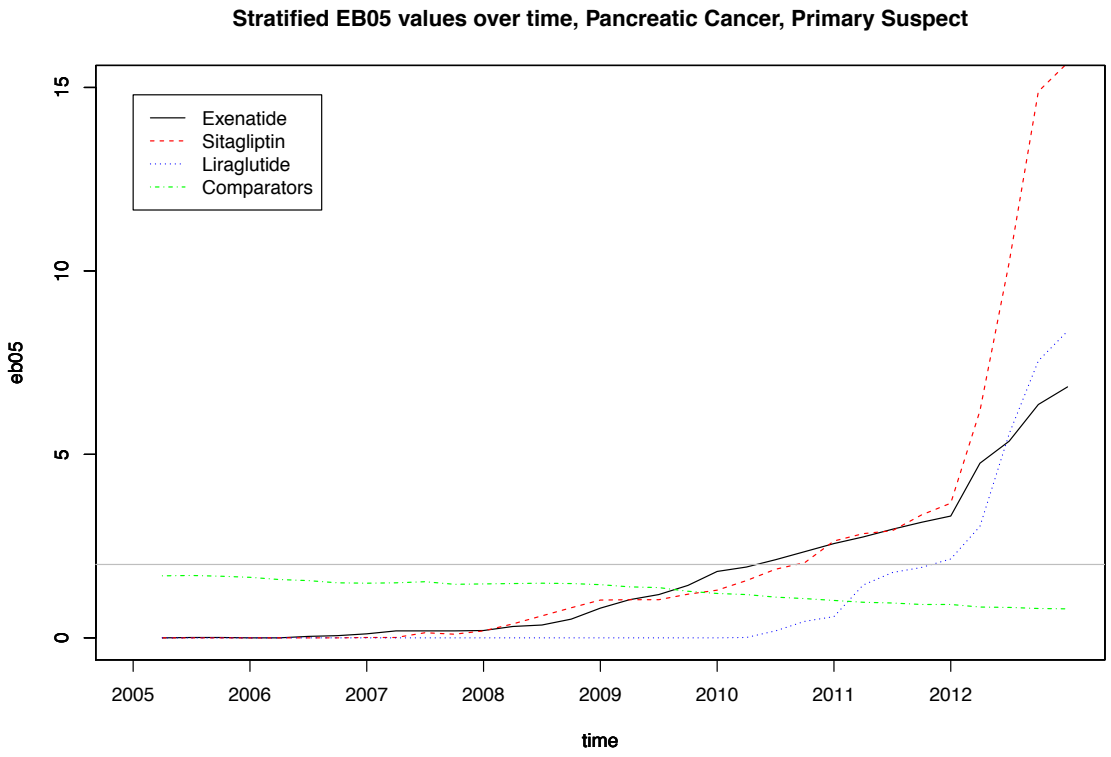


Figure 2. Stratified EB05 analysis for the pancreatic cancer where the target drug is listed as the primary suspect.

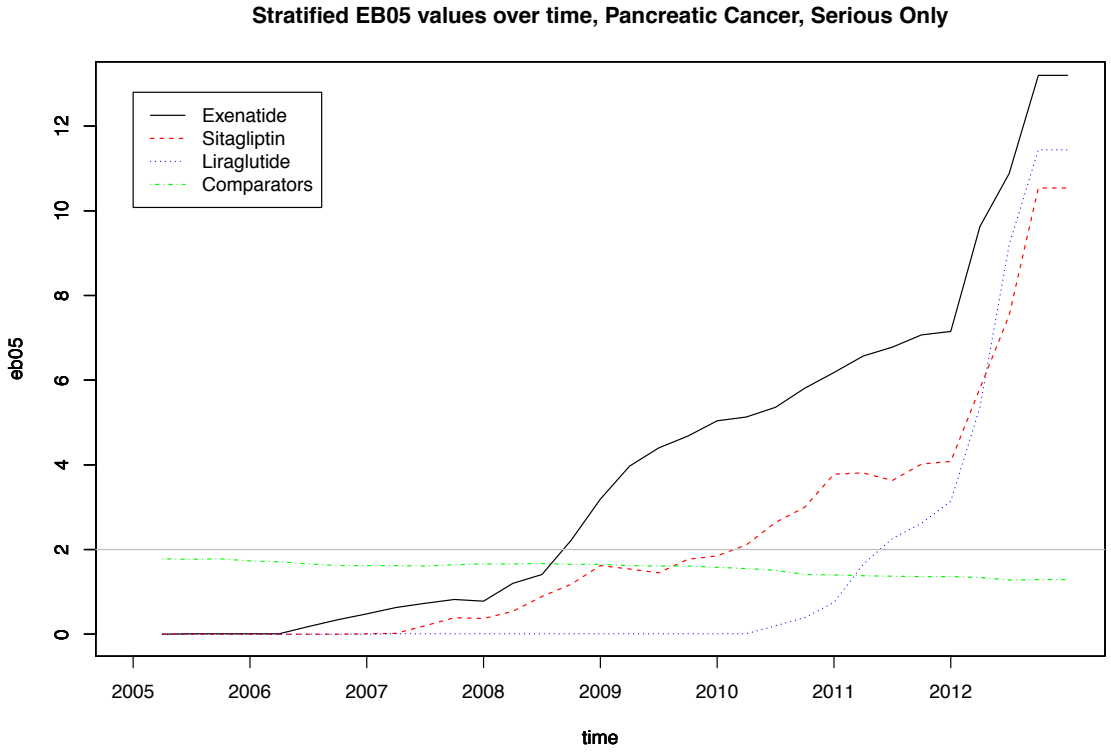


Figure 3. Stratified EB05 analysis for pancreatic cancer restricted to "serious" reports.

39. Both analyses provide results similar to those in Figure 1, although the suspect-only and serious-only analyses yield stronger signals.

40. Figure 4 restricts the analysis to reports emanating from the United States.

41. Some authors have suggested that metformin may reduce the risk of cancer. Recent evidence from randomized trials appears to demonstrate that this is not the case.[31] Nonetheless, I also ran the analyses corresponding to Figure 1 through 4 excluding metformin and glucophage from the comparator list. I provide these statistics in the accompanying spreadsheet. This omission has little or no impact on the comparator analysis.

[31] Stevens, R. J., Ali, R., Bankhead, C. R., Bethel, M. A., Cairns, B. J., Camisasca, R. P., & Holman, R. R. (2012). Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials. *Diabetologia*, 55(10), 2593-2603.

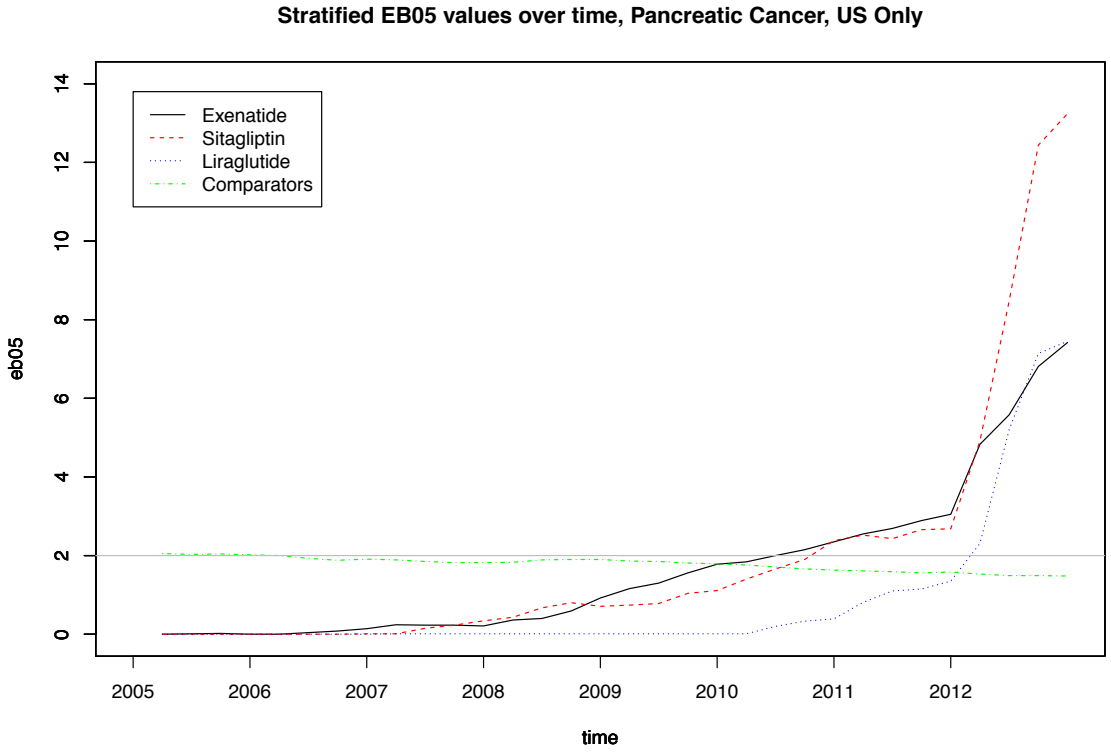
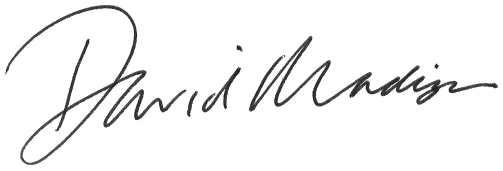


Figure 4. Stratified EB05 analysis for pancreatic cancer restricted to U.S. reports.

6. Conclusion

42. Evidence that exposure to GLP-1 agents could cause pancreatic cancer has existed for many years. Against that backdrop, routine analyses of spontaneous reports show a clear safety signal has existed since at least as far back as 2011 and as far back as 2008 according to company documents. My analysis shows a safety signal for exenatide in the second quarter of 2010, for sitagliptin in the third quarter of 2010, and for liraglutide in the first quarter of 2011. No such signal arises for other anti-diabetic agents. This should have resulted in decisive action by the company.



December 14th, 2014

APPENDIX 1: Selected Spontaneous Report Analyses Driving Withdrawal/Labeling Decisions

Drug: Varenicline (Chantix)

Drug Type: Partial Cholinergic Nicotinic Agonist

Approval: May 2006

Adverse Effects Reported: Neuro-psychiatric issues

Withdrawal: n/a (boxed warning)

References:

FDA. "Public Health Advisory: FDA Requires New Boxed Warnings for the Smoking Cessation Drugs Chantix and Zyban".

http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm170906.htm

Drug: Ticrynafen (Selacryn)

Drug Type: Diuretic

Approval: May 1979

Adverse Effects Reported: Liver toxicity

Withdrawal: January 1980

References:

Ticrynafen recalled. FDA Drug Bulletin 1980;10:3-4.

Zimmerman HJ et al. Ticrynafen-associated hepatic injury: Analysis of 340 cases. Hepatology 1984;4:315- 23.

Chitturi S, George J. Hepatotoxicity of commonly used drugs: Nonsteroidal anti-inflammatory drugs, antihypertensives, antidiabetic agents, anticonvulsants, lipid-lowering agents, psychotropic drugs. Semin Liver Dis 2002;22:169-83.

Drug: Benoxaprofen (Oraflex in US, Opren in UK)

Drug Type: NSAID

Approval: June 1982 (US)

Adverse Effects Reported: Liver and kidney toxicity

Withdrawal: August 1982

References:

Brass EP. Hepatic toxicity of antirheumatic drugs. Cleve Clin J Med 1993;60:466-72.

Marshall E. Guilty plea puts oraflex case to rest. Lancet 1985;229:1071.

Justice deputy barred lilly reps' prosecution. Journal Record 1985;September 13, 1985:NOPGCIT.

Oates JA et al. Clinical implications of prostaglandin and thromboxane A2 formation. New England Journal of Medicine 1988;319:689-98.

Taggart HM. Fatal cholestatic jaundice in elderly patients taking benoxaprofen. British Medical Journal 1982;284:1372.

Goudie BM et al. Jaundice associated with the use of benoxaprofen [letter]. Lancet 1982;1:959.

Drug: Zomepirac (Zomax)

Drug Type: NSAID

Approval: October 1980

Adverse Effects Reported: Anaphylaxis

Withdrawal: March 1983 (Dear Doctor in April 1982)

References:

Corre KA, Spielberg TE. Adverse drug reaction processing in the United States and its dependence on physician reporting: Zomepirac (Zomax) as a case in point. Annals of Emergency Medicine 1988;17:145-9.

Drug: Nomifensine

Drug Type: antidepressant

Approval: January 1985

Adverse Effects Reported: Immune hemolytic anemia

Withdrawal: January 1986

References:

Lessons from nomifensine. Lancet 1988;November 5th:1059-60.

Salama A, Mueller-Eckhardt C. The role of metabolite-specific antibodies in nomifensine-dependent immmune hemolytic anemia. New England Journal of Medicine 1985;313:469-74.

Drug: Suprofen

Drug Type: NSAID

Approval: January 1986

Adverse Effects Reported: Renal flank pain syndrome

Withdrawal: May 1987

References:

Rossi AC et al. The importance of adverse reaction reporting by physicians. Journal of the American Medical Association 1988;259:1203-4.

Drug: L-tryptophan

Drug Type: Nutritional supplement

Approval:

Adverse Effects Reported: Eosinophilia-myalgia syndrome

Withdrawal: November 1989

References:

Eidson M et al. L-tryptophan and eosinophilia-myalgia syndrome in New Mexico. Lancet 1990;335:645-8.

Belongia EA et al. An investigation of the cause of the eosinophilia-myalgia syndrome associated with tryptophan use. New England Journal of Medicine 1990;323:357-65.

Drug: Temafloxacin

Drug Type: Quinolone antibiotic

Approval: February 1992

Adverse Effects Reported: Hypoglycemia and hemolytic anemia

Withdrawal: June 1992

References:

Davey P, McDonald T. Postmarketing surveillance of Quinolones, 1990 to 1992. Drugs 1993;45:46-53.

Drug: Mibefradil (Posicor)

Drug Type: Calcium channel blocker

Approval: August 1997

Adverse Effects Reported: Drug-drug interactions

Withdrawal: June 1998

References:

Roche, FDA announce new drug-interaction warnings for mibefradil. Am J Health-Syst Pharm 1998;55:210.

Painkiller: How a drug apaproved by the FDA turning into a lethal failure---despite early doubts, duract carried a mild warning; then, some patients died---'A lot of wishful thinking'. The Wall Street Journal 1998;Eastern Edition:A1.

Drug: Bromfenac

Drug Type: NSAID

Approval: July 1997

Adverse Effects Reported: Liver injury

Withdrawal: June 1998 (Dear Doctor, February 1998)

References:

Painkiller: How a drug apaproved by the FDA turning into a lethal failure---despite early doubts, duract carried a mild warning; then, some patients died---'A lot of wishful thinking'. The Wall Street Journal 1998;Eastern Edition:A1.

Drug: Grepafloxacin (Raxar)

Drug Type: Quinolone antibiotic

Approval: August 1997

Adverse Effects Reported: Cardiac arrhythmia

Withdrawal: October 1999

References:

Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. Journal of Antimicrobial Chemotherapy 2000;45:557-9.

Glaxo Wellcome voluntarily withdraws raxar (Grepafloxacin). FDA 1999;October 26th.

Drug: Rotavirus vaccine

Drug Type: Vaccine

Approval: August 1998

Adverse Effects Reported: Intussusception

Withdrawal: July 1999

References:

Murphy TV et al. Intussusception among infants given an oral rotavirus vaccine. New England Journal of Medicine 2001;344:564-72.

Centers for Disease Control. Intussusception among recipients of rotavirus vaccine-United States, 1998-1999. Journal of the American Medical Association 1999;282:520-1.

Centers for Disease Control. Withdrawal of rotavirus vaccine recommendation. Journal of the American Medical Association 1999;282:2113-4.

Drug: Cisapride

Drug Type: Gastrointestinal pro-motility agent

Approval: 1993

Adverse Effects Reported: Cardiac effects

Withdrawal: January 2000

References:

Smalley WE et al. Contraindicated use of cisapride: The impact of an FDA regulatory action. Journal of the American Medical Association 2000;284:3036-9.

Drug: Troglitazone

Drug Type: Oral antidiabetic agent

Approval: March 1997

Adverse Effects Reported: Acute liver failure

Withdrawal: March 2000

References:

Graham DJ et al. Liver enzyme monitoring in patients treated with troglitazone. Journal of the American Medical Association 2001;286:831-3.

Hirsch IB. First, do no harm. Clin Diab 2000;18:97-9.

Henney JE. Withdrawal of troglitazone and cisapride. Journal of the American Medical Association 2000;283:2228.

Drug: Baycol

Drug Type: Statin

Approval: June 1997

Adverse Effects Reported: Rhabdomyolysis

Withdrawal: August 2001

References:

Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. Curr Control Trials Cardiovasc Med 2001;2:205-207.

Psaty BM, Furberg CD, Ray WA, Weiss NS (2004). "Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of cerivastatin and risk of rhabdomyolysis". *JAMA* **292** (21): 2622–31.

Drug: Raptiva

Drug Type: Psoriasis

Approval: October 1993

Adverse Effects Reported: Progressive multifocal leukoencephalopathy

Withdrawal: April 2009

References:

Major, E. (2010). "Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies". *Annual Review of Medicine* **61** (1): 35–47.

EXHIBIT B

PREEMPTION EXPERT REPORT

G. Alexander Fleming, M.D.

TABLE OF CONTENTS

I. QUALIFICATIONS AND CREDENTIALS

My name is G. Alexander Fleming, M.D. I received my M.D. degree in 1977 from Emory University School of Medicine in Atlanta, Georgia. My internship and residency in internal medicine were completed from 1977 to 1980 at Emory University Affiliated Hospital.

I completed my Fellowship in Endocrinology from 1980 to 1982 at Vanderbilt University School of Medicine in Nashville, Tennessee. My Fellowship in Metabolism was completed at the National Cancer Institute of the National Institutes of Health in Bethesda, Maryland from 1982 to 1985.

I have been board certified in Internal Medicine since 1981, and board certified in the subspecialty of Endocrinology and Metabolism since 1984.

My 12-year tenure with the Food and Drug Administration (FDA) began in 1986 as a Medical Officer in the Division of Metabolism and Endocrine Drug Products (DMEP). I became the Supervisory Medical Officer in 1989, a position I held until I retired from the agency as its senior endocrinologist in 1998.

I was responsible for the regulation of diabetes and other metabolic drugs at FDA from 1990 to 1998. I am familiar with the FDA regulations governing the approval of drugs and drug labeling, and the practices employed by FDA for such approval. Since leaving the agency, I have remained familiar with and current on FDA labeling regulations and requirements, including in particular the regulation establishing requirements for prescription drug labeling, 21 CFR § 201.57, as well as the regulation governing supplemental applications to revise labeling, 21 CFR § 314.70.

As head of the clinical reviewers of endocrine and metabolic treatments at FDA (which includes drugs for diabetes treatment), I approved the first statins, growth hormones, and all diabetes drugs in the 1990s up to the time I retired from FDA. One of the drugs I approved was metformin, which is still generally regarded as the initial drug of choice for treatment of Type 2 diabetes. All of those approvals included approval of the labeling. I was responsible for review, revision, approval or denial of proposed label changes for all drugs in the Metabolic Group.

My duties at FDA also included representing the agency at international initiatives such as the International Conference on Harmonisation (ICH), where I was a member of three working groups. The ICH seeks to harmonize drug regulatory efforts on a global basis. I was also stationed as the FDA representative at the World Health Organization (WHO) in Geneva from

1992 to 1993. I served as Chair of the Professional Education and Training programs for the FDA's Center for Drug Development and Research (CDER), and co-founded and served as Editor-in-Chief of CDER's *Virtual Journal of Drug Evaluation*. I was also a major contributor to the FDA's Good Review Practice (GRP) initiative, which sought to establish principles, standards, and practices for the review of drug safety and effectiveness.

I have published in medical and scientific journals on the subjects of diabetes treatment and federal regulation of food, drugs, and medical devices, and have written several book chapters on similar topics. The most recent chapter, "Regulatory Considerations for Early Clinical Development," is included in Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development, to be published by Springer in January 2015. I authored the book, Optimizing Therapeutic Development in Diabetes, published in 2000. I have also frequently presented proposals in public meetings for increasing the speed and efficiency of the therapeutic development process. I am a well-known advocate and expert on the "large simple trial" concept as a means of harnessing "real world" clinical data to address both drug efficacy and safety issues at a faster rate than is currently possible with conventional approaches. I also repeatedly advocate in invited lectures what is called an adaptive or step-wise approval process. This approach would allow therapies to be approved sooner for selective populations and would speed the overall availability of therapies to patients based on specific strength of evidence.

I have often been asked to serve as an expert witness in litigation and arbitration cases, but I have only occasionally accepted these invitations. Cases that involved my testimony, either at trial or by deposition within the last four years, include *Unimed Pharmaceuticals, Inc. et al. v. Watson Pharmaceuticals, Inc.*, Civil Action No. 1:03-CV-2501-TWT, in the United States District Court for the Northern District of Georgia, and *Abbott Laboratories v. Lupin Pharmaceuticals, Inc.*, Civil Action No. 09-152-LPS, in the United States District Court for the District of Delaware. I was a consultant to Merck in its litigation related to Vioxx, but was not deposed. I currently support the clinical, regulatory, and/or business strategies of approximately 20 programs in the metabolic therapeutic area, including therapies for pre-diabetes, diabetes and its complications, obesity, elevated lipids and other cardiovascular risk factors, sarcopenia, and rare inborn errors of metabolism. My *curriculum vitae* is included as Appendix A.

When I retired from FDA, I became the Senior Vice President for Global Regulatory Affairs at Worldwide Clinical Trials in Washington, D.C. This company later became Ingenix

Pharmaceutical Services, where I also served as Chief Scientific Officer until June 2002. In July 2002, I co-founded Kinexum LLC, and have served as its Chief Executive Officer continuously since that time. Kinexum provides a wide range of expertise and services for supporting the advancement of new healthcare products toward commercialization. Though much of Kinexum's work involves metabolic drugs, it has supported cardiovascular, oncology, neurology, immunology, and dermatology programs. Modalities include not just pharmaceuticals but cell and gene therapies, medical devices and diagnostics, dietary supplements, and medical foods. Kinexum has supported over 200 companies since its founding.

In 2006, I co-founded Exsulin, which is developing peptide-based drugs targeted at regenerating the insulin-producing islets in patients with both Type 1 and Type 2 diabetes. Exsulin currently has a drug in Phase II clinical trials. This effort requires in depth understanding of the biology of the pancreas. Complicated safety and efficacy issues are involved in this program, and are closely related to those of the incretin drug products. I have served as Chairman of Exsulin's Board of Directors and its Chief Medical Officer since I co-founded the company.

I am also a principal or significant equity holder in several other drug development companies including Ammonett, Thetis, and Diasome. I am co-inventor of composition of matter patent US2014/0364500, published December 11, 2014, for Ursolic Acid Salts for Treating Diabetes and Obesity.

I serve as a Board Member, Advisory Panel Member, or consultant to a number of other pharmaceutical and medical device companies, including Novartis, Pfizer, Lexicon, Sanofi-Aventis, Takeda, and Teva. I have served in the past as an advisor to several of the incretin pharmaceutical companies, including Amylin and Novo. In this capacity, I have frequently advised companies on FDA clinical development and regulatory strategy and diabetes research and the clinical environment. I go back to my former division frequently in support of large and small companies. My last visit was on December 11, 2014. It is part of my practice to maintain my expertise on not only technical matters and FDA regulation, but to understand how individuals and divisions within FDA "think" and act.

Regarding Amylin, while I was still at the FDA, I was responsible for clinical review of the IND for pramlintide (Symlin) and the IND for exenatide (Byetta). After I left the agency, Amylin asked me to help with the NDA submissions for both from 2000–2006, and thereafter

occasionally until 2010. For example, in May 2004, I served as the "External FDA Expert" as part of Amylin's "Mock Submission Review" team for exenatide's NDA.

Regarding Novo, I served on one high level advisory board and consulted with them on several project specific boards from roughly 1999 until 2009, including a Type 1 diabetes immunomodulator, their insulin analogs, Prandin, and Victoza (liraglutide). With regard to liraglutide, I consulted on their Phase 2 and Phase 4 trials, as well as their IND, NDA, and fast-track drug application. I also consulted Novo with regard to the c-cell tumor findings.

I have also advised the manufacturers of other GLP-1 agonists and DPP-4 inhibitors that have been approved in the EU but not the US.

The documents provided to me by counsel, or that I reviewed independently from various sources, including but not limited to the FDA website, are listed in Appendix B to this report. The exhibits attached to this report are listed in Appendix C. Based on my review of the above-referenced documents and my training and experience, I have a number of opinions that are further described below. All of the opinions in this report are given to a reasonable degree of scientific, medical and regulatory certainty. I am being compensated at the rate of $600 per hour for my work on this matter. I reserve the right to supplement this report in light of new information or developments with respect to the issues addressed herein.

In this report, I use the term "Amylin" to refer to one or more of the following corporate entities including Amylin Pharmaceuticals, LLC, formerly known as Amylin Pharmaceuticals, Inc., its affiliates and subsidiaries that are or were involved in the production and sale of Byetta with Lilly. The term "Lilly" refers to Eli Lilly and Company, its affiliates and its subsidiaries that are or were involved in the production and sale of Byetta with Amylin. The term "Merck" refers to Merck Sharp & Dohme Corp and Merck & Co., Inc., its affiliates and its subsidiaries that are or were involved in the production and sale of Januvia and Janumet. The term "Novo" refers to Novo Nordisk, Inc., its affiliates and its subsidiaries that are or were involved in the production and sale of Victoza.

II. INTRODUCTION

I have been asked to discuss and offer opinions about issues relating to the labeling of prescription drugs, including the FDA's process and methods for health risk assessments, health hazard evaluations, safety reporting requirements, and labeling review. It is my understanding that the manufacturers of several incretin drugs contend, as one of their recent legal papers

stated, "the [NEJM Statement] and the FDA's denial of the Victoza Citizen's Petition constitute 'clear evidence that the FDA would not have approved a change' to Defendants' labels to warn of pancreatic cancer."[1]

A large body of statutes and regulations relate to the labeling of prescription drugs, but I am not offering legal interpretations of those laws. Rather, I will address the actual *practices* of the FDA, informed by my training and experience both at the FDA and in the private sector. When I discuss laws and regulations, I do so to explain their use in practice. I rely frequently on the FDA's Guidance documents, as do the FDA and the companies that manufacture the incretin drugs.[2]

The FDA generally does not take an adversarial position against drug manufacturers when it comes to informing the medical community and the public about a drug's potential risks. FDA encourages manufacturers to provide useful drug safety information and very seldom prevents them from providing it.[3] FDA expects manufacturers to identify potential risks and to ensure that physicians and patients have accurate information about such risks, whether through prescribing information, patient monographs, Dear Doctor letters, advertisements, or other means. Manufacturers and the FDA may disagree regarding the wording and prominence of risk information, but it is exceedingly uncommon for the FDA to disagree with a manufacturer's decision to *disclose* a risk at all.[4]

It is important to understand that new drugs are approved on the basis of limited safety information. When a new drug is approved by FDA or any other authority, it is well understood that the drug's labeled safety profile is preliminary. A decade or more of study during the

---

[1] *In Re Incretin-Based Therapies Product Liability Litigation*, Case No.13md2452. Dkt. 822 (December 1, 2014) p. 6.

[2] See, e.g., deposition of Novo's Regulatory Liaison, Thompson Deposition, p. 64:15 –65:12 ("The information in the label is – it's really determined by the **guidances** that tell you where it's appropriate to include the information. … It's based on review of the guidance and it **-- the guidance details what information is appropriate in the different sections of the labe**l.") (emphasis added).

[3] It is my understanding that Plaintiffs asked the incretin manufacturers to identify any circumstance they knew of where such a prohibition had actually occurred, and they refused to answer. If any examples of such prohibitions are forthcoming, I will gladly review and comment on them in light of my experience at the FDA and in the private sector.

[4] Manufacturers will often request the use of language that describes a risk in less direct terms than the FDA may suggest, and will similarly often request that language describing a risk be placed in a less prominent location than that suggested by FDA.

marketing of a drug may be required to establish a drug's safety profile. The bargain FDA provides to manufacturers is that it will approve therapies with only preliminary evidence of safety and effectiveness. In return, manufacturers are expected to continuously—and typically without the guidance of FDA— identify and pursue the resolution of safety signals that may reflect significant adverse effects of the drug.

I have seen no indication here that the FDA would have prevented the incretin manufacturers from informing physicians and patients that pancreatic cancer is a potential risk of the incretin mimetics. Any action by the FDA to preclude the disclosure of such risk information (e.g., FDA's rejection of a CBE accompanied by a statement to the effect that any incretin mimetic incorporating pancreatic cancer risk information in its label would be considered misbranded) would be far outside the usual practices of the agency and inconsistent with its well-known tendency to be conservative in matters of drug safety and adequately informing prescribers. That is particularly the case in DMEP, my former division at FDA, as mentioned above. FDA rejection of an appropriately worded and supported CBE would also be contrary to several of FDA's own Guidance documents, which encourage pharmacovigilance to be directed toward "serious, unlabeled adverse events."[5]

I understand that an argument is being made that the FDA would have rejected a CBE addressing a pancreatic cancer risk because of comments made in the New England Journal of Medicine (NEJM) article of February 27, 2014[6] and FDA's March 25, 2014 response to the Citizen's Petition regarding Victoza[7] In my view, this reflects a fundamental misunderstanding of how the FDA functions as an organization, the role the FDA plays with respect to drug safety, and the way the FDA approaches prescription drug labeling.

One of the FDA's roles is to communicate with prescribing physicians and the public about risks associated with drugs available in the marketplace. The NEJM article was such a communication, informing physicians and the public that it is aware of recent media and

[5] Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. (March 22, 2005) p. 6 ("FDA recommends that emphasis usually be placed on review of serious, unlabeled adverse events….").

[6] Egan, A., et al., Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment. N.Eng.J.Med. 2014 Feb. 27; 370(9): 794-797.

[7] Ltr. from U.S. Food and Drug Administration to Public Citizen. (March 25, 2014) available online at: http://www.citizen.org/documents/2020_FDA%20Final%20Response%20to%20Petition.pdf.

scientific attention directed to the effect that incretin medications have on the pancreas; that it has detected a pancreatic safety signal; that it has not reached a final conclusion; and that it is continuing to monitor the situation. The NEJM article manifestly does not discuss the submission of a CBE regarding the risk of pancreatic cancer, nor how FDA might react to such a submission.

Similarly, FDA's response to the Victoza Citizen's Petition indicates only that FDA will not require pancreatic cancer risk information to be added to the Victoza label based on the information currently available to FDA. As with the NEJM article, FDA's response to the Petition does not discuss the possibility of a CBE submission about the risk of pancreatic cancer, and does not say how FDA would respond to one.

When the FDA does not want a manufacturer to include information on a label, it does so in a standard manner by serving a formal, written notice upon the manufacturer that describes what may be placed on the label, followed by an advisement that the drug may be considered to be misbranded if it is marketed with the proposed label before FDA approval.[8] In the absence of that advisement in response to a specific adverse reaction or warning proposal at hand, there is no sound basis on which to predict the FDA would consider a particular adverse reaction or warning to be a "misbranding" of the drug.

The manufacturers' argument that they can predict FDA's response to a pancreatic cancer CBE based solely on the NEJM article and the response to the Victoza Citizen's Petition is not sound, because it does not reflect an understanding of the issues, the context, and the actual practices at FDA. There is no reason to believe the agency would have rejected a CBE in the past, or would reject a CBE in the present or the future, merely because, at some point, the FDA had considered an issue and had decided not to *mandate* a warning. Rather, FDA would comply with its statutory obligations and thoroughly review both the language used in the CBE and the supporting science. As explained further below, to prohibit all risk information relating to pancreatic cancer would be extremely unusual and not in accordance with the FDA's actual practices and the ways of thinking in DMEP.

The NEJM article and FDA's response to the Victoza Citizen's Petition demonstrate an ongoing interest at FDA in the pancreatic safety of incretin medications. That ongoing interest provides no basis to conclude that FDA would actively prohibit all risk information about

[8] See e.g., LILLY02159687.

pancreatic cancer. To the contrary, FDA's continuing interest in the pancreatic safety of the incretin drugs suggests that it would be very receptive to efforts by the incretin manufacturers to inform the medical community and the public about the risk of pancreatic cancer. With the Public Safety Communication, the NEJM article, and the two Rouse study publications, the FDA has now on several occasions informed the public that it believes there is a plausible causal association between incretin mimetics and pancreatic cancer in humans. Those same four publications also specifically state that the FDA is continuing to investigate that link.

Additionally, it is important to understand that the over 4,000 people involved in drug regulation at FDA do not form a monolith. Individuals and divisions within FDA have their specific roles and often have differences in opinions. I am prepared to describe what the role of the NEJM article was in the larger picture of incretin drug product regulation, and will explain how the "FDA" could both state that "current knowledge is adequately reflected in the product information or labeling," while also being receptive, rather than hostile, to a label change that adds pancreatic cancer risk information.

Within this framework, my report discusses three principal opinions. First, the incretin mimetic[9] manufacturers have available to them information that would support a label change to address the risk of pancreatic cancer associated with their drugs. Second, the manufacturers' information could have been used to support a label change regarding pancreatic cancer. Third, the available regulatory history demonstrates that FDA would not have prohibited the manufacturers from adding to their labels information addressing the risk of pancreatic cancer associated with the incretin medications.

III. BACKGROUND

A. DIABETES: WHAT IS IT AND HOW IS IT TREATED?

Diabetes mellitus, often referred to simply as diabetes, is a condition that disrupts the body's normal metabolism of sugars and fats, which leads to elevated blood glucose levels and other abnormalities. Very elevated glucose levels can present immediate danger, but milder

[9] For the sake of convenience and to conform with the FDA's convention of referring to all of the drugs involved in this case as "incretin mimetics," that term will be used throughout this report. As explained later in the report, only the GLP-1 agonists (exenatide and liraglutide) actually mimic the body's incretin hormones. The DPP-4 inhibitor (sitagliptin) does not mimic the incretin hormones, but rather acts to slow the rate at which those hormones break down.

elevations can go unnoticed. Over time, elevated blood sugar and fat levels can cause a number of devastating complications involving the heart, circulation, kidney, eyes, and nerves. In the U.S., diabetes is the most common cause of blindness, renal failure, and amputations. It is a major cause of heart attacks and other heart problems.

There are two principal types of diabetes. Only about 5% of people with diabetes have Type 1 diabetes, in which the body does not produce any insulin at all. Insulin is a hormone the body needs in order to convert sugars, starches and other foods into energy that can be used by the muscles and other tissues. It essentially acts as a "key" that "unlocks" the body's cells and allows them to absorb blood sugar. Type 1 diabetics experience high blood sugar levels because their bodies do not produce the insulin necessary to allow their blood sugar to be absorbed by the cells and used for energy. Left untreated, high blood sugar levels can lead to significant complications such as heart disease, stroke and kidney failure. Treatment for Type 1 diabetes usually involves injections of insulin timed to coincide with the rise in blood sugar that occurs shortly after eating.

There are two principal types of diabetes. Only about 5% of people with diabetes have Type 1 diabetes, in which the body does not produce any insulin at all. Insulin is a hormone the body needs in order to transport glucose, a simple sugar, from the blood stream into cells where it is the key energy source. Glucose is consumed in the diet in the form of simple and complex carbohydrates, which are broken down into glucose in the GI track. If insulin is not present, glucose cannot be utilized as an energy source by the muscles and other tissues. The glucose levels rise in the blood and this leads to tissue damage. Insulin essentially acts as a "key" that "unlocks" the body's cells and allows them to internalize the bloods glucose. Type 1 diabetics experience a complete absence of insulin because the insulin secreting cells in the pancreas are destroyed by immune attack. Extremely high blood sugar levels in Type 1 diabetic patients if they go without insulin treatment for more than a few hours. Left untreated, high blood sugar levels can lead to significant complications such as heart disease, stroke and kidney failure. Treatment for Type 1 diabetes usually involves injections of insulin timed to coincide with the rise in blood sugar that occurs shortly after eating.

B. SUMMARY OF TYPE 2 DIABETES TREATMENTS

This section will briefly discuss the medications used to treat Type 2 diabetes over the last century up until the present. Many treatment options are now available for people in the U.S.

with Type 2 Diabetes, buy until the approval of metformin in 1994, the only major options were insulin secretagogues (most of which were sulfonylurea compounds), and unmodified human and animal insulins. Acarbose, a glucosidase inhibitor that slows the breakdown of carbohydrates into sugars was approved in 1995. "Modern" insulin secretagogues (Amaryl, Prandin) soon followed. What might be considered as marking the beginning of the era of novel or modern therapies for diabetes was the approval of the first rapid acting insulin analogue (Humalog) in 1996 and the first long acting insulin analog (Lantus) in 2000. Modern classes of oral therapies followed. The first of the glitzones, Rezulin, was approved in 1997 and was followed by Avandia (2001) and Actos (2002) Rezulin was later removed from the market. The first approved incretin class was that of the DPP-4 inhibitors (Januvia [first in class approved in 2006], Nesina, Onglyza, Tradjenta). The second incretin class is comprised by the glucagon-like peptide (GLP) analogs. Byetta, the first of the GLP analogs (Bydureon, Tanzeum, Trulicity, and Victoza) was approved in 2005. There is a less known incretin class formed by the amylin mimetics. Pramlintide (Symlin), another injected peptide hormone product works through a different receptor, but its effect is similar to other incretins. Though Symlin is approved for both Type 1 and 2 patients, it is not often used.

The most recent class to be approved are the sodium-glucose co-transporter 2 (SGLT2) inhibitors. These include Invokana (canaglifozin—first to market, approved in 2013), dapagliflozin (Farxiga), and Jardiance (empagliflozin. SGLT-2 inhibitors work by blocking glucose from being reabsorbed by the kidneys, which results in glucose being lost in the urine and lower blood glucose levels.

Combinations of the above approved drugs have become popular. They combine different medications in one pill—including metformin and a sulfonylurea, a DPP4 inhibitor, or a thiazolidinedione, or a thiazolidinedione in combination with a sulfonylurea. This reduces the number of pills a patient has to take. Combination drugs include Actoplus MET, Avandamet, Duetact, Glucovance, Metaglip, and PrandiMet.

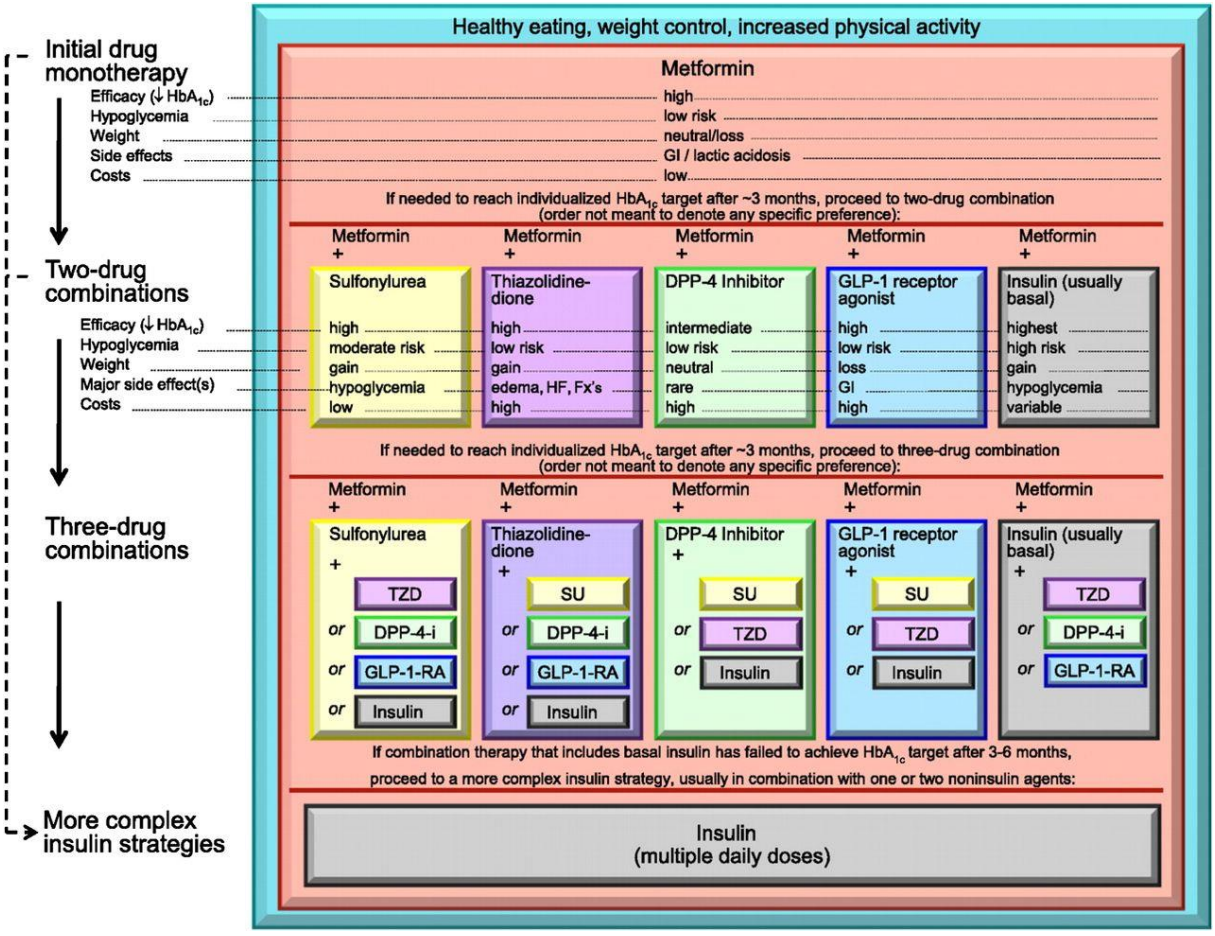
C. THE THERAPEUTIC APPROACH TO TYPE 2 DIABETES

When Type 2 diabetes is first diagnosed, glucose levels can be well controlled with metformin or sulfonylurea or a combination of metformin with sulfonylurea, DPP-4 inhibitor, or a glitazone. Over time, additional therapies are typically required. The recent addition of the SGLT-2 class has provided yet another oral therapy option. Most patients and physicians want to avoid use of insulin and some of these patients will opt to start injected GLP-1 agonist treatment. Long acting

insulin analog treatment (Lantus, Detimir) has become popular because it carries less risk of low blood glucose levels. The important point here is that many different drug choices are available to people with Type 2 diabetes. The major diabetes professional organizations have issued recommended algorithms for initiating and adding medications. An example is shown in the table[10] below:

American Diabetes Association

Anti-hyperglycemic therapy in type 2 diabetes: General recommendations.



[10] American Diabetes Association. Standards of Medical Care in Diabetes – 2014. Diabetes Care. Jan 2014; 37(1): S14 – S80 p. S27.

D. HISTORY OF DRUG PRODUCTS FOR DIABETES

1. Insulin

Perhaps the most important moment in the history of diabetes treatment was the discovery of insulin in 1922-23.[11] Insulin is a "hypoglycemic" agent, because it reduces glucose levels in the blood (blood sugar). As noted above, insulin acts as a key that unlocks the body's cells, allowing blood sugar to enter the cells and provide energy to the body. Since its discovery, insulin has been life-saving for Type 1 diabetes patients who are totally insulin deficient. Many Type 2 patients become dependent on insulin therapy. Because insulin is taken by injection, most Type 2 patients avoid taking it until they have no other way of controlling glucose levels.[12]

2. Non-Insulin Hypoglycemic Agents

a. The Biguanides

There are many other hypoglycemic agents besides insulin. The biguanides are a class of hypoglycemic drugs also used to treat diabetes. These drugs do not affect the body's output of insulin, but generally increase the body's sensitivity to insulin. This results in lower blood sugar levels as more cells respond to the body's insulin and allow blood sugar to be processed for energy. The biguanides also reduce the amount of glucose released from the liver, which reduces the amount of glucose in the blood, in turn lowering blood sugar levels. The biguanides are taken orally.[13]

Two of the biguanides, **phenformin** and **buformin**, have been withdrawn from the market because of their association with lactic acidosis, a potentially serious side effect. Another biguanide, **metformin**, is now the only drug in this class still in clinical use. **Metformin** has a 30-year track record of efficacy, safety and low cost, and is widely viewed as the initial drug of

[11] Banting, FG., et al., Pancreatic Extracts in the Treatment of Diabetes Mellitus. Preliminary Report. Can.Med.Assoc.J. 1922; 12: 141-146.
[12] See generally, Mayo Clinic, Diabetes Treatment: Using Insulin to Manage Blood Sugar, available online at: http://www.mayoclinic.org/diseases-conditions/diabetes/in-depth/diabetes-treatment/art-20044084.
[13] Bailey, C.J., Biguanides and NIDDM, Diabetes Care, 1992 Jun; 15(6):755-772.

choice for treatment of Type 2 diabetes.[14] **Metformin** has been used in Europe since the 1970s. It was approved by me for use in the United States in 1995 when I was at the FDA.[15]

b. The Sulfonylureas

Another class of hypoglycemic drugs, the sulfonylureas, lower blood sugar levels by increasing the release of insulin from the pancreas. The sulfonylureas can induce weight gain, and can also cause hypoglycemia (low blood sugar) under certain conditions (e.g., if the dosage is too high or the patient is fasting). This class of drugs includes **chlorpropamide**, **glyburide**, **glipizide** and **glimepiride**. The sulfonylureas are taken orally. Despite the many new diabetes therapies that have been discovered over the past 50 years, metformin and the sulfonylureas are still two of the most popular initial choices for treatment of Type 2 diabetes, though the use of sulfonylureas is falling.

c. The Thiazolidinediones

The thiazolidinediones are a more recent class of hypoglycemic drugs. They are usually referred to as the "TZDs" or "glitazones," and were introduced in the late 1990s. These drugs decrease insulin resistance and also decrease glucose output from the liver, both of which have the effect of lowering blood sugar. They are taken orally, and used in the treatment of Type 2 diabetes.

Ciglitazone was the first TZD to be evaluated, but it was associated with hepatotoxicity (chemically driven liver damage) and was never marketed. Other TZDs developed later include **pioglitazone** (Actos), **troglitazone** (Rezulin) and **rosiglitazone** (Avandia). **Troglitazone** (Rezulin) was removed from the market, again because of an association with hepatotoxicity**. Rosiglitazone** (Avandia) was temporarily removed from the market because of an association with increased cardiovascular events, but is available again for use on a limited basis. **Pioglitazone** (Actos) continues to be under investigation because of an association with bladder cancer. Both **rosiglitazone** and **pioglitazone** can cause substantial fluid retention, which can lead to congestive heart failure. Because of these and other safety concerns, use of TZDs has fallen

[14] Drucker, D., et al., Sitagliptin Nature Reviews Drug Discovery 2007. Glucagon 2007 Feb; 6:109 - 110.

[15] Susan M. Cruzan, FDA Approves New Diabetes Drug (Press release). (December 30, 1994), available online at: http://web.archive.org/web/20070929152824/http://www.fda.gov/bbs/topics/ANSWERS/ANS00627.html.

dramatically. It was once thought that this drug class could help to prevent or reverse Type 2 diabetes. This is an example of how the accumulation of evidence during marketing can dramatically change a drug's safety profile.

d. Other Diabetes Medications

Less commonly used medications for Type 2 diabetes include Acarbose, which is known for causing gas and indigestion, Symlin, which is provides modest efficacy and requires injection, and bromocriptine, which is an oral drug but has attracted little use. The new SGLT-2 class r is becoming popular because of its weight loss promoting effect and relatively good tolerability.

E. HISTORY OF THE INCRETIN MIMETICS

The defendants in this case manufacture two different types of drugs: GLP-1 agonists and DPP-4 inhibitors. Both of these act to lower blood sugar in Type 2 diabetics, but they do so in different ways.

1. GLP-1 Agonists

GLP-1 is glucagon-like peptide-1, a hormone that triggers the release of insulin by the pancreas. An "agonist" is a chemical that binds to a receptor and activates it. GLP-1 agonists work by binding to GLP-1 receptors in the pancreas, stimulating the pancreas to secrete insulin. This release of insulin then allows the body's cells to absorb more blood sugar, reducing the body's blood sugar levels. The GLP-1 agonists are sometimes referred to as "incretin mimetics" because they mimic the function of the incretin hormones in the gastrointestinal tract. The incretin term refers to the property of a hormone or drug to *increase* the secretion and action of insulin.

There are now several GLP-1 agonists on the market. This case involves two of them: **exenatide** (**Byetta** and **Bydureon**); and **liraglutide** (**Victoza**). Like other GLP-1 agonists, they are used to treat Type 2 diabetes, and both are administered by injection.

a. Exenatide (Byetta and Bydureon)

Byetta was approved by the FDA in 2005 and marketed by Amylin Pharmaceuticals and Eli Lilly.[16] It is typically injected twice per day.[17] Bydureon is an extended-release formulation of exenatide approved in January 2012.[18] It is administered by injection once per week.[19]

b. Liraglutide (Victoza)

Victoza was approved by the FDA in 2010 and marketed by Novo Nordisk.[20] It is administered by injection once per day.[21]

2. DPP-4 Inhibitors

DPP-4 is dipeptidyl peptidase-4, an enzyme that plays a major role in the body's metabolism because it quickly breaks down the incretin hormones (including GLP-1) that stimulate the production of insulin. DPP-4 inhibitors work by blocking the DPP-4 enzyme. This delays the enzyme's breakdown of the GLP-1 hormone, allowing GLP-1 to trigger further insulin secretion. The release of additional insulin in turn allows the cells to absorb more blood sugar, lowering the body's blood sugar levels.[22]

---

[16] Ltr. from U.S. Food and Drug Administration to Amylin Pharmaceuticals Approving NDA 21-773 (April 28, 2005), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2005/021773ltr.pdf.

[17] Byetta Approval Label. (April 28, 2005), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021773lbl.pdf.

[18] Ltr. from U.S. Food and Drug Administration to Amylin Pharmaceuticals Approving NDA 22-200. (January 27, 2012), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022200Orig1s000_corrected_ltr.pdf.

[19] Bydureon Approval Label. (January 27, 2012), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200Orig1s000lbledt.pdf.

[20] Ltr. from U.S. Food and Drug Administration to Novo Nordisk Approving NDA 22-341. (January 25, 2010), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022341s000ltr.pdf.

[21] Victoza Approval Label (January 25, 2010) available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022341lbl.pdf

[22] The DPP-4 inhibitors are not true "incretin mimetics" because, unlike the incretin hormones, they do not *directly* stimulate the production of insulin. The DPP-4 inhibitors do so *indirectly* by delaying the breakdown of the incretin hormones. Despite this distinction, the FDA refers to both GLP-1 agonists and DPP-4 inhibitors as "incretin mimetics," and that term is used in this report as well. Both the GLP-1 agonists and DPP-4 inhibitors are sometimes also referred to as "incretin-based therapies."

There are several DPP-4 inhibitors on the market, but the only one involved in this case is **sitagliptin** (**Januvia** and **Janumet**).

a. Sitagliptin (Januvia and Janumet)

Januvia was the first DPP-4 inhibitor brought to market. It was approved by the FDA in October 2006 and marketed by Merck.[23] It is taken orally once per day.[24]

Janumet is a combination of **sitagliptin** and **metformin**. It was approved by the FDA in April 2007 and also marketed by Merck.[25] It is typically taken orally twice a day.[26]

IV. THE MANUFACTURER OF A DRUG, NOT THE FDA, HAS THE PRIMARY RESPONSIBILITY FOR THE DRUG'S SAFETY AND THE ADEQUACY OF ITS LABEL

The drug companies, not FDA, are responsible for alerting the medical community, potential prescribers and patients to the risks associated with their drugs. This responsibility applies equally, if not more so, to those risks which are unknown or poorly understood by FDA, or for which FDA lacks complete and accurate information. Manufacturers cannot simply wait to provide risk information to doctors and patients until FDA requires them to do so.

The theme that manufacturers are responsible for their labels is repeated throughout the Food, Drug and Cosmetic Act (FDCA) and FDA regulations. *See, e.g.*, 21 CFR § 201.57(c)(6) (requiring drug manufacturers, not FDA, to revise a label's "warnings and precautions" section "as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established"); 21 CFR § 201.57(c)(7) (requiring manufacturers, not FDA, to describe in a label's "adverse reactions" section "all … adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event"); 21 CFR § 314.70 (describing procedures by which manufacturer, not FDA, may change its drug's label with or without prior approval by FDA); 21 CFR § 314.80 (requiring drug

[23] Ltr. from U.S. Food and Drug Administration to Merck Approving NDA 21-995. (October 16, 2006), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021995s000ltr.pdf.
[24] Januvia Approval Label. (October 16, 2006), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021995lbl.pdf.
[25] Ltr. from U.S. Food and Drug Administration to Merck Approving NDA 22-044. (March 30, 2007), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/022044s000ltr.pdf.
[26] Janumet Approval Label. (March 30, 2007), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022044lbl.pdf.

manufacturers, not FDA, to review and report post-marketing adverse events); 73 Fed. Reg. 49605 ("a sponsor cannot contend that, because the Secretary has the power to order new labeling changes, the sponsor no longer has an obligation to monitor post-marketing experiences and maintain its labeling under applicable Federal regulations.").[27]

Requiring manufacturers to be responsible for their labels is appropriate because they are in the best position to monitor the safety of their drugs, and they have the resources to do it. It is widely recognized that the FDA's resources for monitoring the thousands of drugs now on the market are limited. Recent studies on this topic have reached the same conclusion as those done decades ago: the FDA does not have sufficient resources to adequately monitor drug safety.[28] [29]

Drug manufacturers often obtain important safety information well before FDA does, and they have access to information that is not available to FDA. The scientists and physicians employed by a manufacturer to create, develop, market and study a drug often do so over a period of many years, and can be expected to develop an understanding of the drug's potential

[27] The same point has been made by the United States Supreme Court when addressing the responsibilities of drug manufacturers under the FDCA. *See, e.g., Wyeth v. Levine*, 555 U.S. 555, 570-71 (2009) ("throughout many amendments to the FDCA and FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times.").

[28] For instance, in 1955 an FDA advisory committee found "conclusively" that "the budget and staff of the Food and Drug Administration are inadequate to permit the discharge of its existing responsibilities for the protection of the American public." Citizens Advisory Committee on the FDA, Report to the Secretary of Health, Education, and Welfare, H.R. Doc. No. 227, 84th Cong., 1st Sess., 53. Over 50 years later in 2007, the National Academies, Institute of Medicine, in The Future of Drug Safety: Promoting and Protecting the Health of the Public, 193-194, found that "The [FDA] lacks the resources needed to accomplish its large and complex mission … There is widespread agreement that resources for postmarketing drug safety work are especially inadequate and that resource limitations have hobbled the agency's ability to improve and expand this essential component of its mission." This again is a problem explicitly recognized by the Supreme Court. *See, e.g., Wyeth v. Levine*, 555 U.S. at 578-79 and n.11.

[29] For real-world numbers, I know from my experience while at FDA and afterward that the review and ongoing regulation of a new drug involves a professional staff at FDA of roughly three dozen people. Each of these professionals also has responsibilities for many other investigative and approved drugs. I also know from my consulting experience with major pharmaceutical companies that a typical Type 2 drug program may involve as many as 1000 professionals at the peak period of development, and perhaps several hundred professionals who stay involved over the drug's life cycle. Many of these professionals are entirely dedicated to the single drug program. These huge differences in resources illustrate why FDA could never be expected to bear the responsibility for a drug product's postmarket safety evaluation and product labeling.

safety profile that is more informed than FDA's. What a drug company knows about its drug is always far greater than what the FDA knows.

The duties of a drug manufacturer are therefore informed not only by the FDCA and FDA regulations, but also by what the manufacturer knew or should have known about the risks presented by its drugs. The incretin manufacturers are responsible for the safety of their drugs regardless of what the FDA did or did not do.

V. OVERVIEW OF FDA APPROVAL FOR NEW DRUGS

A. THE FDA APPROVAL PROCESS AND REQUIREMENTS

A drug cannot be introduced into interstate commerce unless its manufacturer has shown the drug is safe and effective for its intended conditions of use. 21 U.S.C. § 355. The FDA approves a drug if there are "adequate and well-controlled" clinical trials that demonstrate the drug's safety and effectiveness for those intended conditions of use. 21 U.S.C. § 355(d)(7). The "intended conditions" for the use of a drug are listed in its labeling, which is reviewed and approved by the FDA. 21 U.S.C. §§ 355(d)(1) and (2). Any indications for use that are not listed in a drug's labeling have not been approved by the FDA.[30]

B. STANDARDS GOVERNING LABEL DISCLOSURES

I address the following standards based on my experience working at the FDA from 1986 to 1998, having written about food and drug law, having trained other FDA employees in food and drug law, and having dealt with FDA statutes and regulations extensively while at the FDA and afterward in my work with drug manufacturing companies.

In 1979, FDA, as part of a final rule titled "Labeling and Prescription Drug Advertising: Content and Format for Labeling for Human Prescription Drugs"[31] issued 21 CFR §§ 201.57(e) and (g) which stated, respectively:

> (e) **Warnings**: Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them and steps that should be taken if they occur. **The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of**

[30] "The labeling is derived from the data submitted with the new drug application. It presents a full disclosure summarization of drug use information, which the supplier of the drug is required to develop from accumulated clinical experience and systemic drug trials of preclinical investigations and adequate, well-controlled clinical investigations that demonstrate the drug's safety and the effectiveness it purports or is represented to possess." 37 Fed. Reg. 16,503 (1972).
[31] 44 Fed. Reg. 37434 (June 26, 1979).

> **a serious hazard with a drug; a causal relationship need not have been proved.**
>
> (g) **Adverse Reactions**: An adverse reaction is an **undesirable effect reasonably associated with the use of the drug** that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. [32]

(Emphasis added.) In 2006, FDA made several revisions to the above language and issued the final rules for 21 CFR §§ 201.57(c)(6) and (7). Those rules now state the following:

> (c)(6) 5 **Warnings and precautions.** (i) General. This section must describe clinically significant adverse reactions…. **In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.** (Emphasis added.)
>
> (c)(7) 6 **Adverse reactions.** This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, **an adverse reaction is an undesirable effect, reasonably associated with use of a drug**, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those **adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.** (Emphasis added.)

The above rules and related FDA commentary help inform what a drug manufacturer is required to do in order to fulfill its responsibility for the safety of its drug and the adequacy of its label for that drug.

C. STANDARDS GOVERNING A DRUG MANUFACTURER'S RESPONSIBILITY FOR INVESTIGATING THE SAFETY OF ITS DRUG

A number of FDA regulations address specific duties assigned to drug manufacturers in order to maximize the likelihood that they will not only become aware of safety issues with their drugs, but also report those issues to FDA. For instance, FDA regulations require that a drug's manufacturer carefully review safety information pertinent to its drugs, regardless of the source of that information:

> **A sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources,** including information derived from any clinical or epidemiological

[32] 44 Fed. Reg. 37434 (June 26, 1979) at 37465.

> investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

21 CFR § 312.32(b) (emphasis added). The regulations similarly require prompt reporting of potentially serious risks that arise with a drug:

> **The sponsor must notify FDA and all participating investigators** (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report **of potential serious risks, from clinical trials or any other sources, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting** under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

21 CFR § 312.32(c)(1) (emphasis added). There are detailed regulations addressing the reporting needs for adverse reactions:

> **The sponsor must report any suspected adverse reaction that is both serious and unexpected.** The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as: (A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g. angioedema, hepatic injury, Stevens-Jonson Syndrome); (B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture); (C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

21 CFR § 312.32(c)(1)(i)(A-C) (emphasis added). Similar rules apply to the reporting of safety information derived from epidemiological studies and other sources, regardless of who performed the studies:

> **The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies** (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and **whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.** Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

21 CFR § 312.32(c)(1)(ii) (emphasis added). The same applies to findings from animal or in vitro testing that suggest any significant risk to humans:

> **The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans** exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.

21 CFR § 312.32(c)(1)(iii) (emphasis added).

Manufacturers must also "report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure." 21 CFR § 312.32(c)(1)(iv). They are required to "notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information." 21 CFR § 312.32(c)(2). A manufacturer must also "promptly investigate all safety information it receives." 21 CFR § 312.32(d)(1). "Relevant followup information to an IND safety report must be submitted as soon as the information is available and must be identified as such[.]" 21 CFR§ 312.32(d)(2).

Manufacturers are also responsible for meeting annual reporting requirements. 21 CFR § 314.81(b)(2). Within 60 days of the anniversary of the U.S. approval of the application, the manufacturer must submit an annual report to the FDA division responsible for reviewing the application. The summary shall contain, among other things, the following:

> A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study.

21 CFR § 314.81(b)(2)(i). 21 CFR § 314.81(b)(2) also requires reporting of additional information regarding nonclinical laboratory studies, clinical data and trials, postmarketing study commitments and postmarketing studies.

VI. FDA REGULATORY HISTORY FOR THE INCRETIN MIMETICS

This section addresses several of the specific regulatory actions taken by the FDA with respect to each of the drugs involved in this case. The focus is on actions that give insight into how the FDA would respond to a CBE adding pancreatic cancer risk information to a drug's

label, or observations that inform this discussion. This section does not address every FDA regulatory action taken with respect to each drug.

A. FDA REGULATORY HISTORY FOR BYETTA

1. Byetta's Approval

Byetta (chemical name exenatide) was approved on April 28, 2005 "to improve glycemic control in patients with Type 2 diabetes mellitus who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea."[33] Byetta was the first incretin-based therapy approved by FDA.

2. October 2007 FDA Exenatide – Information for Healthcare Professionals: Exenatide (marketed as Byetta) – 10/2007

In October 2007, FDA issued an alert entitled *Information for Healthcare Professionals: Exenatide (marketed as Byetta) – 10/2007*.[34] FDA noted the following:

> FDA has reviewed 30 postmarketing reports of acute pancreatitis in patients taking Byetta, a drug used to treat adults with Type 2 diabetes. An association between Byetta and acute pancreatitis is suspected in some of these cases.
>
> Healthcare professionals should instruct patients taking Byetta to seek prompt medical care if they experience unexplained persistent severe abdominal pain which may or may not be accompanied by vomiting. If pancreatitis is suspected, Byetta should be discontinued. If pancreatitis is confirmed, Byetta should not be restarted unless an alternative etiology is identified.
>
> FDA has asked and the maker of Byetta, Amylin Pharmaceuticals, Inc. has agreed to include information about acute pancreatitis in the PRECAUTIONS section of the product label.

3. August 18, 2008 FDA Exenatide – Information for Healthcare Professionals Update

On August 18, 2008, FDA issued an update to its October 2007 alert.[35] FDA stated the following:

---

[33] Ltr. from U.S. Food and Drug Administration to Amylin Pharmaceuticals Approving NDA 21-773. (April 28, 2005), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2005/021773ltr.pdf.

[34] U.S. Food and Drug Administration, FDA Alert: Information for Healthcare Professionals: Exenatide (marketed as Byetta) – 10/2007. (October 2007), available online at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124712.htm.

[35] U.S. Food and Drug Administration, FDA Alert: Information for Healthcare Professionals: Exenatide (marketed as Byetta) – 8/2008 Update. (August 18, 2008), available online at:

> Since issuing Exenatide (marketed as Byetta) - Information for Healthcare Professionals (10/2007) in October 2007, FDA has received reports of 6 cases of hemorrhagic or necrotizing pancreatitis in patients taking Byetta. Byetta is a medicine given by subcutaneous injection to help treat adults with Type 2 diabetes. Of the 6 cases of hemorrhagic or necrotizing pancreatitis, all patients required hospitalization, two patients died and four patients were recovering at time of reporting. Byetta was discontinued in all 6 cases.
>
> Byetta and other potentially suspect drugs should be promptly discontinued if pancreatitis is suspected. There are no known patient characteristics which determine when pancreatitis associated with Byetta will be complicated by the hemorrhagic or necrotizing forms of this condition. If pancreatitis is confirmed, initiate appropriate treatment and carefully monitor the patient until recovery. Byetta should not be restarted. Consider antidiabetic therapies other than Byetta in patients with a history of pancreatitis.
>
> FDA is working with the maker of Byetta, Amylin Pharmaceuticals, Inc., to add stronger and more prominent warnings in the product label about the risk of acute hemorrhagic or necrotizing pancreatitis.

4. <u>November 2, 2009 FDA Information for Healthcare Professionals: Reports of Altered Kidney Function in patients using Exenatide (Marketed as Byetta)</u>

On November 2, 2009, FDA issued an Information for Healthcare Professionals entitled *Reports of Altered Kidney Function in patients using Exenatide (Marketed as Byetta).*[36] Specifically, FDA stated the following:

> FDA has approved revisions to the drug label for Byetta (exenatide) to include information on post-marketing reports of altered kidney function, including acute renal failure and insufficiency.
>
> Byetta, an incretin-mimetic, is approved as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus.
>
> From April 2005 through October 2008, FDA received 78 cases of altered kidney function (62 cases of acute renal failure and 16 cases of renal insufficiency), in patients using Byetta. Some cases occurred in patients with pre-existing kidney disease or in patients with one or more risk factors for developing kidney problems. From April 2005 through September 2008, more than 6.6 million

---

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm.

[36] U.S. Food and Drug Administration, Information for Healthcare Professionals: Reports of Altered Kidney Function in Patients Using Exenatide (Marketed as Byetta). (November 2, 2009), available online at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm188656.htm.

prescriptions[1] for Byetta were dispensed. Therefore, the 78 reported cases of altered renal function represent a small percentage of the total number of patients who have used the drug.

Some of the 78 patients reported nausea, vomiting, and diarrhea--the most common side effects associated with Byetta in clinical trials. These side effects may have contributed to the development of altered kidney function in the reported cases.

The revisions to the drug label allow healthcare professionals to better weigh the known benefits of Byetta with the potential risks that exist for certain patients. Changes include:

- Information regarding post-market reports of acute renal failure and insufficiency, highlighting that Byetta should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) or end-stage renal disease.
- Recommendations to healthcare professionals that caution should be applied when initiating or increasing doses of Byetta from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min).
- Recommendations that healthcare professionals monitor patients carefully for the development of kidney dysfunction, and evaluate the continued need for Byetta if kidney dysfunction is suspected while using the product.
- Information about kidney dysfunction in the patient Medication Guide to help patients understand the benefits and potential risks associated with Byetta.

5. Byetta Safety Update for Healthcare Professionals

On November 9, 2009, FDA issued a *Byetta Safety Update for Healthcare Professionals*.[37] In the *Update*, FDA noted:

> As part of our ongoing efforts to keep you informed, we want to make you aware of recent safety information for Byetta, an anti-diabetic drug. On October 30, 2009, FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for Byetta. The REMS was part of an approval for a new indication of Byetta to be used as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus. Previously Byetta was only approved for use in combination with other anti-diabetic drugs.

[37] U.S. Food and Drug Administration, *Byetta Safety Update for Healthcare Professionals* (November 9, 2009), available online at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190406.htm.

The REMS is the result of new safety information associated with the use of Byetta, including postmarketing reports of acute pancreatitis and altered kidney function. Acute pancreatitis was previously listed in the prescribing information for Byetta, but more severe forms of pancreatitis, including hemorrhagic and necrotizing pancreatitis, have been reported to FDA since the initial label update. FDA issued safety communications on these adverse event reports in 2007 (acute pancreatitis), 2008 (hemorrhagic and necrotizing pancreatitis) and 2009 (altered kidney function).

Over 7 million prescriptions for Byetta have been dispensed since it was first approved by FDA in 2005. Therefore, while these adverse events are very serious, the number of reported cases of acute pancreatitis, hemorrhagic and necrotizing pancreatitis, and altered kidney function represent a small percentage of the total number of patients who have used Byetta.

To ensure that healthcare professionals and patients fully understand the benefits and potential risks associated with the use of Byetta, the REMS contain several elements including:

- A *Medication Guide* given to patients each time they receive a prescription for Byetta from a pharmacy. The Medication Guide explains the benefits and risks associated with using Byetta
- A *Communication Plan* requiring the manufacturer of Byetta to distribute a Dear Healthcare Professional letter discussing the potential for altered kidney function to occur in patients using Byetta
- Evaluating healthcare professional and patient understanding of the potential for acute pancreatitis and altered kidney function in patients using Byetta
- Additionally, the sponsor, Amylin Pharmaceuticals Inc., is being required to conduct six post-marketing studies *(Postmarketing Requirements* [PMRs]) to help further define the mechanism, incidence, and risk factors for the development of acute pancreatitis, including hemorrhagic and necrotizing pancreatitis, associated with the use of Byetta, as well as to explore a potential signal of a serious risk of thyroid cancer and pancreatic cancer.

B. FDA REGULATORY HISTORY FOR JANUVIA AND JANUMET

1. Januvia and Janumet's Approval

Januvia (chemical name sitagliptin) was approved on October 16, 2006 "as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes mellitus as monotherapy and in combination with metformin or a PPAR agonist (e.g., thiazolidinediones)

when diet and exercise plus the single agent do not provide adequate glycemic control."[38] Januvia is also an incretin-based therapy, but unlike Byetta, which is a GLP-1 agonist, Januvia is a DPP-4 inhibitor. While Byetta is a larger molecule composed of peptides that requires injection, Januvia is a smaller molecule that is taken as an oral pill.

Janumet (chemical name sitagliptin/metformin) was approved on March 30, 2007 "as an adjunct to diet and exercise to improve glycemic control in adult patients with Type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin."[39] Janumet, like Januvia, is again an incretin-based therapy.

2. September 25, 2009 Information for Healthcare Professionals – Acute pancreatitis and sitagliptin (marketed as Januvia and Janumet)

On September 25, 2009, FDA issued an Information for Healthcare Professionals entitled *Acute pancreatitis and sitagliptin (Marketed as Januvia and Janumet).*[40] Specifically, FDA stated the following:

> FDA is revising the prescribing information for Januvia (sitagliptin) and Janumet (sitagliptin/metformin) to include information on reported cases of acute pancreatitis in patients using these products.
>
> Sitagliptin, the first in a new class of diabetic drugs called dipeptidyl peptidase-4 (DPP-4) inhibitors, is approved as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus.
>
> Eighty-eight post-marketing cases of acute pancreatitis, including two cases of hemorrhagic or necrotizing pancreatitis in patients using sitagliptin, were reported to the Agency between October 16, 2006 and February 9, 2009. Based on these reports, FDA is working with the manufacturer of sitagliptin and sitagliptin/metformin to revise the prescribing information to include:

---

[38] Ltr. from U.S. Food and Drug Administration to Merck Approving NDA 21-995 (October 16, 2006), p. 1, available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021995s000ltr.pdf.

[39] Ltr. from U.S. Food and Drug Administration to Merck Approving NDA 22-044. (March 30, 2007), p. 1, available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/022044s000ltr.pdf.

[40] U.S. Food and Drug Administration *Information for Healthcare Professionals – Acute Pancreatitis and Sitagliptin (marketed as Januvia and Janumet)* (September 25, 2009), available online at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm.

- Information regarding post-marketing reports of acute pancreatitis, including the severe forms, hemorrhagic or necrotizing pancreatitis.
- Recommending that healthcare professionals monitor patients carefully for the development of pancreatitis after initiation or dose increases of sitagliptin or sitagliptin/metformin, and to discontinue sitagliptin or sitagliptin/metformin if pancreatitis is suspected while using these products.
- Information noting that sitagliptin has not been studied in patients with a history of pancreatitis. Therefore, it is not known whether these patients are at an increased risk for developing pancreatitis while using sitagliptin or sitagliptin/metformin. Sitagliptin or sitagliptin/metformin should be used with caution and with appropriate monitoring in patients with a history of pancreatitis.

3. February 17, 2012 FDA Warning Letter to Merck Regarding Noncompliance with Timetables for Competition of Postmarketing Study and Milestone Dates

On February 17, 2012 FDA issued a *Warning Letter* to Merck concerning Januvia and Janumet.[41] The FDA stated:

> The U.S. Food and Drug Administration (FDA) has determined that your firm failed to comply with the milestone dates, within a previously agreed-upon timetable for completion, to conduct a required postmarketing study (PMR) for the purpose of investigating a safety issue associated with the use of Januvia® and Janumet® under New Drug Applications (NDA) 021995 and 022044, respectively. Failure to comply with the milestone dates, and to demonstrate good cause for your noncompliance, is in violation of section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 355].
>
> This violation is concerning from a public health perspective because the PMR milestone dates (as described below) constitute part of a written agreement between you and the FDA to conduct additional testing to further assess a signal of a serious risk of acute pancreatitis, including necrotizing forms, associated with the use of sitagliptin.

The FDA concluded:

> Under section 502(z) of the Act [21 U.S.C. 352(z)], your product is considered misbranded because you are in violation of a postmarketing requirement (PMR) established under section 505(o)(3) of the Act. You have failed to comply with the approved timetable and periodic report submissions of section 505(o)(3)(E)(ii)

[41] Warning Ltr. from U.S. Food and Drug Administration to Merck (February 17, 2012), available online at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm293490.htm.

of the Act and failed to show good cause for not conducting the additional testing required to further assess whether a signal of a serious risk of acute pancreatitis, including necrotizing forms, associated with the use of sitagliptin, represents a public health risk.

C. FDA REGULATORY HISTORY FOR VICTOZA

1. Victoza's Approval

Victoza (chemical name liraglutide) was approved on January 25, 2010 "as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus."[42] Victoza is also an incretin-based therapy and, like Byetta, is a GJP-1 agonist.

2. Victoza's Risk Mitigation Strategy

In January 2010 FDA approved a REMS (Risk Evaluation and Mitigation Strategy) for Victoza. The most recent REMS modification was in July 2014. A REMS is a strategy required by FDA "to manage known or potential serious risks associated with a drug product to ensure the benefits of a drug outweigh its risks." According to the REMS:

> The goal of the VICTOZA REMS is to mitigate the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with VICTOZA by:
>
> - Informing healthcare providers about the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with VICTOZA .

As stated in the REMS, the purpose of the VICTOZA REMS is to inform healthcare providers about the following serious risks:

> Potential Risk of Medullary Thyroid Carcinoma
>
> - Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether VICTOZA causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies.
>
> Risk of Acute Pancreatitis
>
> - Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with VICTOZA .

[42] Ltr. from U.S. Food and Drug Administration to Novo Nordisk Approving NDA 022341 (January 25, 2010), p. 1, available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022341s000ltr.pdf.

- In clinical trials studying VICTOZA, there were more cases of pancreatitis in patients treated with VICTOZA than in patients treated with comparators.

3. March 25, 2014 Denial of Public Citizen's April 19, 2012 Citizen's Petition

On April 19, 2012, Public Citizen, a non-profit advocacy group, submitted a Citizen's Petition to the FDA with a very broad demand.[43] The Petition requested that FDA "immediately remove from the market the diabetes drug liraglutide (Victoza; Novo Nordisk) because the known increased risks of thyroid cancer and pancreatitis, both of which occurred in people enrolled in preapproval clinical trials, outweigh any documented clinical benefits." FDA responded on March 25, 2014:

> FDA has carefully considered the information submitted in the Petition, the comments submitted to the docket, and other relevant data identified by the Agency. Based on our review of the information, and for the reasons explained below, your requests are denied. However, as with all FDA-approved products, we will continue to monitor and review available information related to Victoza and take any further action as appropriate.[44]

The FDA's response noted the following regarding pancreatic cancer:

> The Petition states that Victoza increases the risk of pancreatic cancer and cites AERS data to support this finding. Pancreatic cancer is characterized by the National Cancer Institute as a common cancer, i.e., occurring at a rate of greater than 35,000 new cases per year. Analysis of drug-related risk utilizing FAERS data does not provide strong evidence of risk when the adverse event (i.e., pancreatic cancer) occurs commonly in the background untreated population and has a long latency period. Any causal association between exposure to Victoza and pancreatic cancer is indeterminate at this time.
>
> In our review of 49 unique cases recovered from FAERS we found no new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza that would support any changes to the current approved labeling. Therefore, any suspicion of causal association between exposure to Victoza and pancreatic cancer is indeterminate at this time. We will continue to monitor and to review available safety information related to pancreatic cancer in patients who are receiving Victoza.

[43] Ltr. from Public Citizen to Food and Drug Administration (April 19, 2012), available online at http://www.citizen.org/documents/2020.pdf.

[44] Ltr. from U.S. Food and Drug Administration to Public Citizen (March 25, 2014), available online at:
http://www.citizen.org/documents/2020_FDA%20Final%20Response%20to%20Petition.pdf.

D. FDA REGULATORY HISTORY FOR THE INCRETIN MIMETICS DRUG CLASS

1. Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for Type 2 diabetes

On March 14, 2013 FDA issued the following *Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for Type 2 diabetes*.[45] The FDA stated:

> The U.S. Food and Drug Administration (FDA) is evaluating unpublished new findings by a group of academic researchers that suggest an increased risk of pancreatitis, or inflammation of the pancreas, and pre-cancerous cellular changes called pancreatic duct metaplasia in patients with Type 2 diabetes treated with a class of drugs called incretin mimetics. These findings were based on examination of a small number of pancreatic tissue specimens taken from patients after they died from unspecified causes. FDA has asked the researchers to provide the methodology used to collect and study these specimens and to provide the tissue samples so the Agency can further investigate potential pancreatic toxicity associated with the incretin mimetics.
>
> FDA has not reached any new conclusions about safety risks with incretin mimetic drugs. This early communication is intended only to inform the public and health care professionals that the Agency intends to obtain and evaluate this new information. FDA will communicate its final conclusions and recommendations when its review is complete or when the Agency has additional information to report.
>
> FDA previously warned the public about postmarketing reports of acute pancreatitis, including fatal and serious nonfatal cases, associated with the use of the incretin mimetic drugs exenatide and sitagliptin. A recently published study that examined insurance records also found the use of exenatide or sitagliptin could double the risk of developing acute pancreatitis. The *Warnings and Precautions* section of the drug labels and the patient Medication Guides for incretin mimetics contain warnings about the risk of acute pancreatitis. FDA has not previously communicated about the potential risk of pre-cancerous findings of the pancreas with incretin mimetics. Further, FDA has not concluded these drugs may cause or contribute to the development of pancreatic cancer.
>
> **At this time, patients should continue to take their medicine as directed until they talk to their health care professional, and health care professionals should continue to follow the prescribing recommendations in the drug labels.**

[45] U.S. Food and Drug Administration, FDA Drug Safety Communication: FDA Investigating Reports of Possible Increased Risk of Pancreatitis and Pre-cancerous Findings of the Pancreas from Incretin Mimetic Drugs for Type 2 Diabetes. (March 14, 2013), available online at: http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm.

> FDA is continuing to evaluate all available data to further understand this potential safety issue. In addition, FDA will participate in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Cancer Institute's (NCI) Workshop on Pancreatitis-Diabetes-Pancreatic Cancer in June 2013 to gather and share additional information.
>
> FDA urges both patients and health care professionals to report adverse events involving incretin mimetics to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

2. <u>February 27, 2014 Article - Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment, New England Journal of Medicine</u>

On February 27, 2014, the FDA and EMA (European Medicines Agency) published an article in the New England Journal of Medicine entitled *Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment* ("NEJM Article").[46] The article stated:

> Within the past year, the FDA and the EMA independently undertook comprehensive evaluations of a safety signal arising from postmarketing reports of pancreatitis and pancreatic cancer in patients using incretin-based drugs. These investigations, now complete, included examination of data from a 2013 research report revealing a possible pancreatic safety signal. Both agencies committed themselves to assessing the evidence pertinent to reported adverse events, as well as any factors that might confound safety analysis in the context of antidiabetic drugs. Although the disproportionate spontaneous reporting of adverse events is commonly interpreted as a safety signal, there are inherent limitations to the ability to establish causal relationships, including the evaluation of events with high background rates, long latency periods, or a possible contribution by the disease itself.

In its concluding paragraph, the authors wrote:

> Thus, the FDA and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal. The FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling, and further harmonization among products is planned in Europe. Ongoing strategies include systematic capture of data on pancreatitis and pancreatic cancer from

[46] Egan, A., et al., Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment. N.Eng.J.Med. 2014 Feb. 27; 370(9): 794-797.

> cardiovascular outcome trials and ongoing clinical trials, which should facilitate meta-analyses, and accumulation of further knowledge regarding these signals in the future.

With respect to determining whether the incretin mimetics play a causal role in the development of pancreatic cancer or pancreatitis, the article stated that "[t]he FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship."

3. Current FDA Website

The most current information made available to medical professionals and patients on the FDA's website regarding the association between the incretin mimetics and pancreatic cancer is its March 14, 2013 communication, in which FDA states:

> FDA has not reached any new conclusions about safety risks with incretin mimetic drugs. This early communication is intended only to inform the public and healthcare professionals that the Agency intends to obtain and evaluate this new information. FDA will communicate its final conclusions and recommendations when its review is complete or when the Agency has additional information to report.[47]

Neither the NEJM article nor FDA's response to the Victoza Citizen's Petition are mentioned on the FDA's web page for the incretin mimetics.[48] This is significant because the FDA's website, among other things, is designed to be a tool for communicating important drug safety information to the medical community, potential prescribers and the public.

VII. OVERVIEW OF FDA PROCESS FOR LABEL CHANGES BY CBE

FDA regulations allow manufacturers to change a drug's label to "add or strengthen a contraindication, warning, precaution, or adverse reaction" in order to reflect newly acquired information about a drug's safety. 21 CFR § 314.70(c)(6)(iii).[49] For certain label changes the manufacturer wants to institute immediately the manufacturer can submit a "Supplement – Changes Being Effected" *Id*., and "may commence distribution of the drug product involved

---

[47] U.S. Food and Drug Administration, FDA Drug Safety Communication: FDA Investigating Reports of Possible Increased Risk of Pancreatitis and Pre-cancerous Findings of the Pancreas from Incretin Mimetic Drugs for Type 2 Diabetes. (March 14, 2013), available online at: http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm.

[48] http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm343516.htm.

[49] "New safety information" is defined broadly under the FDCA, and includes "information derived from a clinical trial, an adverse event report, a postapproval study … peer-reviewed biomedical literature … or other scientific data deemed appropriate by the Secretary…." 21 U.S.C. § 355-1(b)(3).

upon receipt by the agency of a supplement for the change." 21 CFR § 314.70(c)(6). Otherwise, a manufacturer can submit a "Supplement – Changes Being Effected in 30 Days." 21 CFR § 314.70(c)(3). That gives the agency notice of the change, and the agency can choose to act if it sees fit, or the change will go into effect in 30 days. Typically, if the agency responds to a CBE that includes warning information, it does so with a proposal for minor wording changes, or with a request for enhanced prominence.

In this case, the Changes Being Effected (CBE) process could be used to add risk information about pancreatic cancer to different sections of the label: the "warnings and precautions" section and the "adverse reactions" section. Different standards apply to those sections. The applicable standards for each will be addressed in turn.

For the "warnings and precautions" section, the relevant standards for revision of the label are as follows:

> In accordance with §§ 314.70 and 601.12 of this chapter, **the labeling *must* be revised to include a warning about a clinically significant hazard as soon as there is *reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established*.**

21 CFR § 201.57(c)(6)(i) (emphasis added).

For the "adverse reactions" section, the applicable standards do not require "reasonable evidence of a causal association." Rather, the "adverse reactions" section uses a lower standard:

> This section **must** describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, **an adverse reaction is an undesirable effect, *reasonably associated with use of a drug***, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, **only those adverse events for which there is *some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event*.**

21 CFR § 201.57(c)(7) (emphasis added).

VIII. OVERVIEW OF FDA PROCESS FOR *REQUIRING* LABEL CHANGES

Since 2007, the FDA has had statutory authority to require manufacturers to change their labels in response to "new safety information." 21 U.S.C. § 355(o)(4). FDA guidance defines "new safety information" very broadly to include information derived from:

> … a clinical trial, an adverse event report, a postapproval study … peer-reviewed biomedical literature … or other scientific data deemed appropriate by [FDA] about a serious risk or an unexpected risk associated with use of the drug that

> [FDA] has become aware of ***(that may be based on a new analysis of existing information)*** since the drug was approved…

Ex. ___, p. 3 (Guidance for Industry: Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act, July 2013) (all bracketing, bolding and italics in original).[50] The FDA may learn about new safety information from many sources, including:

- Communications with foreign regulatory authorities regarding postmarket analysis of adverse reactions associated with drugs approved in their countries.[51]

- Meta-analyses of safety information, or new analyses of previously submitted information.[52]

Id. at p. 16.

Congress took special care to include a "rule of construction" as part of the statute, ensuring that the FDA's power to *mandate* label changes would not diminish the manufacturer's duty to *update* its label as required:

> **This paragraph shall not be construed to affect the responsibility of the responsible person … to *maintain its label in accordance with existing requirements***, including [21 CFR § 201.57 and related labeling regulations] and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations).

21 U.S.C. § 355(o)(4)(I) (emphasis added).[53]

IX. DISCUSSION OF THE NEJM ARTICLE AND FDA'S RESPONSE TO THE VICTOZA CITIZEN'S PETITION

As discussed briefly in the Introduction, attempting to predict FDA's response to a CBE on the sole basis of the NEJM article and the Citizen's Petition Response — while ignoring the relevant regulatory history, the FDA's other public actions,[54] and the available science —is

[50] Guidance for Industry Safety Labeling Changes-Implementation of Section 505(o)(4) of the FD&C Act (July 30, 2013).

[51] The HealthCanada Signal Assessment fits within this category of new safety information. It is discussed further in Part X.B.1.a, infra.

[52] Dr. David Madigan's statistical analysis fits within this category of new safety information. It is discussed further in Part X.B.2.b, infra.

[53] The validity of this provision was again recognized by the Supreme Court in *Wyeth v. Levine*, 555 U.S. at 567-68 ("Congress … adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels.").

[54] E.g., the Public Safety Communication, which remains open and is the most recent statement actually contained on the FDA's website, as well as the two Rouse studies.

unsound, would not be the practice at the FDA or in private industry, and reflects a fundamental misunderstanding of the roles the FDA fills and the means and methods it uses to fill those roles.

The FDA has two separate and distinct roles: (1) communicating information to the medical community, potential prescribing physicians and the public and (2) monitoring, with a heavy reliance upon the manufacturer's' own diligence, the risks of approved drugs. The NEJM article is plainly an example of (1) alone, that is, the FDA communicating to the medical community and the public that it is aware of recent media and scientific attention, that it has detected a pancreatic safety signal, that it has not reached a final conclusion, and that it is continuing to monitor it.

In reviewing a CBE that included risk information about pancreatic cancer, [55] the FDA does not review the CBE by attempting a dogmatic re-interpretation of a short public statement it made in the past.[56] Rather, the FDA would thoroughly review the CBE and the supporting science, including comprehensive reviews of data and analysis from reputable sources, such as the Health Canada Signal Assessment,[57] and the nonclinical work from its own laboratories, such as the second study published by Rouse et al after the NEJM article. As I explain both above and below, a rejection of, and prohibition of, all risk information relating to pancreatic cancer would be extremely unusual and would not be in keeping with the FDA's actual practices.

The FDA's Public Safety Communication, the NEJM article, the response to the Victoza Citizen's Petition, and the regulatory history for these medications all indicate an ongoing

[55] For purposes of this report, I render my opinions with the underlying assumption, based on the information in this litigation, that none of the manufactures has submitted a CBE to the FDA regarding pancreatic cancer. In light of the evidence discussed in this report, a responsible incretin manufacturer would be compelled to submit a CBE regarding pancreatic cancer. If, in turn, the FDA responded with a rejection of the CBE and the threat of a misbranding prosecution, then there would be a sound basis on which to begin considering that the FDA would have prohibited the manufacturer from using a particular warning.

[56] [redacted]
MRKJAN10000478571-72.

[57] [redacted]

interest at the FDA in resolving the pancreatic safety of incretin mimetics. It is illogical to jump from the conclusion that the FDA has an ongoing interest in the safety of incretin mimetics to the conclusion that the FDA would prohibit all risk information about pancreatic cancer. In addition, if that were the FDA's conclusion, the FDA could have simply stated that it was not going to accept or review any additional pancreatic safety information from the manufacturers, including CBEs. It did not do so. In fact, it did the opposite and confirmed that its investigation was ongoing. This is confirmed not only by the concluding language in the NEJM article, but the last mention on the topic that can be found on the FDA's website: "FDA will communicate its final conclusions and recommendations when its review is complete or when the Agency has additional information to report."

If anything, FDA's continued interest in pancreatic safety shows that it would be very receptive to an effort by the manufacturers to inform the medical community and public of the risk, as the FDA itself has now done twice (the March 14, 2013 *Drug Safety Communication* and the NEJM article), informing the public that it has recognized a signal for pancreatic cancer and it cannot rule out a causal link. The FDA has also published two separate animal studies reiterating concerns about this causal link, and demonstrating scientific evidence supporting such a link.

The FDA's statement in the NEJM article that "[t]he FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling…" does not negate that conclusion. Rather, given the FDA's multiple roles and its actual practices, it is clear that the FDA is merely communicating that it has chosen not to mandate a label change regarding pancreatic cancer based on the information it has received to date. The law that gives the FDA the power to require label changes, 21 U.S.C. § 355(o)(4), is very clear that it is not to be "construed to affect the responsibility of the [manufacturer] to maintain its label in accordance with existing requirements." *Id*. at § 355(o)(4)(I). In other words, FDA's statement reflects its own decision on the labeling for its own purposes, but does not state or imply that a pancreatic cancer CBE from the manufacturers would be rejected.

This conclusion is bolstered by additional language in the same sentence: "and further harmonization among products is planned in Europe." As discussed below, the EMA, shortly before the NEJM article went to print, required all incretin mimetic manufacturers to update their

Risk Management Plans to identify pancreatic cancer as an "important potential risk."[58] [redacted][59] In other words, it makes little sense to assume that by issuing a *joint* statement with the EMA, which required the incretin manufacturers to *add* pancreatic cancer to their Risk Management Plans before the NEJM article was published, that FDA actually meant to adopt a much different posture than the EMA, and instead stifle further investigation or dissemination of information regarding pancreatic cancer.

In addition, and also discussed in more below, [redacted].[60] FDA has shown that it is very interested in Health Canada's analysis and understanding of these drugs, and FDA has shown its concern when the manufacturers have withheld safety information made available to them through Health Canada's regulatory efforts. It would be very unusual for the FDA to prospectively deny an incretin mimetic manufacturer's pancreatic cancer CBE [redacted]

Rather, it would be typical of FDA practice to either accept a pancreatic cancer CBE as-is, or accept it with minor changes to its wording or to its location in the label. This is precisely what the FDA did in response to the manufacturers' CBEs identifying pancreatitis in postmarketing reports, and such a course is far more likely for pancreatic cancer than any hypothetical ban on all risk information about the disease.

X. THE INCRETIN MANUFACTURERS HAVE INFORMATION THAT SUPPORTS A LABEL CHANGE REGARDING PANCREATIC CANCER

All manufacturers are under an affirmative duty to thoroughly investigate all potential risks, and to update their labels accordingly. As described above, the incretin mimetic manufacturers can avail themselves of the CBE process. To fulfill their obligations to update

[58] MRKJAN0001369356, NOVO-00949394, and AMYLN05318927.

[59] [redacted] MRKJAN0002984791, NNI-EMA-00030267. [redacted]

[60] Health Canada Advisement Letter for Januvia. (October 1, 2014), MRKJAN0003072602.

their labels, manufacturers are expected to review information from a broad array of sources. These sources include:

- "controlled trials or epidemiologic studies conducted after marketing approval, manufacturer's safety-related labeling supplements, and other analyses of postmarketing adverse events, including single cases or case series from the literature or from spontaneous reporting"
- "Routine monitoring of Adverse Event Reporting System (AERS)," "Data mining of AERS … databases"
- "Medical literature"
- "Reports of preclinical, toxicological, or pharmacokinetic studies, clinical trials, or observational studies"
- "Studies and clinical trials that may or may not have been conducted as postmarket requirements or commitments or with FDA's knowledge"
- "Communications with foreign regulatory authorities regarding postmarket analysis of adverse reactions associated with drugs approved in their countries;" and
- "Meta-analyses of safety information, or new analyses of previously submitted information."[61,62]

FDA regulations and guidance documents sometimes refer to labeling obligations based on "new safety information." As a practical matter, the distinction between "new" and "old" safety information does not matter in the FDA's analysis, because "new safety information" is statutorily defined to include both new data derived from clinical trials, adverse event reports and other sources, as well as "a new analysis of existing information." 21 U.S.C. § 355-1(b)(3).

An example of this principle is found in the most recent (02/22/13) Final Guidance from the FDA on labeling, the "Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements," which discusses how manufacturers should comply with the "Physician Labeling Rule" (PLR).[63] This is the rule that established the "Highlights" structure now found on all prescribing information sheets. In that Final Guidance,

[61] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006), p. 11.
[62] Guidance for Industry Safety Labeling Changes-Implementation of Section 505(o)(4) of the FD&C Act (July 30, 2013), p. 16.
[63] Guidance for Industry Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (February 22, 2013).

the FDA noted that most labeling changes to the PLR format would not require new studies, but also addressed the importance of new information:

> However, if new information is available that causes the labeling to be inaccurate, the labeling must be updated to incorporate the new information (§ 201.56(a)(2)). In some cases, a reanalysis of the data may be necessary. Furthermore, if essential information is missing from the labeling (e.g., new information about a class drug interaction), this information must be included (§ 201.56(a)(2)).

Guidance on PLR Content and Format p. 3.[64] The point here is that under the FDA's practice, the manufacturer is expected to vigilantly monitor potential safety issues and to bring concerning scientific data — whether new scientific evidence, or a new analysis of existing evidence — to the FDA's attention by way of labeling submissions.

Regardless of when or how a manufacturer obtains safety information, the manufacturer is obligated to thoroughly investigate all potential risks, and to update its label accordingly. Manufacturers have superior resources that are or should be committed to overseeing the safety of the drugs they market. As a result, manufacturers invariably get safety information before the FDA does and have access to information that is not available to the FDA. Company scientists and physicians also develop impressions and understanding of a drug's potential safety profile that can be expected to be more informed than the FDA's.

Risks that are rare, appear as common illnesses, have long latency periods, result from drug interactions, or have adverse impacts on subpopulations, may go undetected in clinical testing. However, if a drug company has reason to suspect a drug may result in adverse events, it has a responsibility to investigate them and to inform physicians and health care providers.

---

[64] Guidance for Industry Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (February 22, 2013), p. 3.This principle was also stated in the Supreme Court's discussion of CBEs in *Wyeth v. Levine*:

> As the FDA explained in its notice of the final rule, **"'newly acquired information'" is not limited to new data, but also encompasses "new analyses of previously submitted data."** *Id*., at 49604. The rule accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments: **"[I]f the sponsor submits adverse event information to FDA, and then later conducts a new analysis of data showing risks of a different type or of greater severity or frequency than did reports previously submitted to FDA, the sponsor meets the requirement for 'newly acquired information.'"** *Id*., at 49607; see also *id*., at 49606.

555 U.S. at 569 (emphasis added.)

When presenting a label submission with a new adverse reaction, or an added or strengthened warning, a company is expected to present to the FDA, in a fair and thorough manner, the evidence it has relating to that adverse reaction or warning.

The FDA Guidance's provide a number of factors to be considered when a manufacturer proposes adding an adverse reaction or warning. As a practical matter, when reviewing a CBE, the type of data considered above can be summarized into the following three general categories:

1. The biological plausibility of the mechanism of the adverse reaction;
2. Evidence of signals that the adverse reaction is occurring, including in animals or humans; and,
3. The seriousness of the adverse reaction.

The manufacturers have or could have had access to a multitude of scientific evidence that could be used to support a label change. Some of this evidence is already in the possession of the FDA, although it is unclear what, exactly, the FDA has reviewed beyond the specific materials referenced in the NEJM article. A manufacturer cannot comply with its obligations by dumping reams of data on the FDA, or by burying pertinent safety information. Rather, it is the duty of the manufacturer to bring to the attention of the FDA pertinent safety information in an unbiased fashion that ensures the FDA has an opportunity to consider it.

I do not believe the NEJM article indicates any intent on the FDA's part to prohibit manufacturers from informing physicians and patients about the potential of their drugs to cause pancreatic cancer. Moreover, the following evidence, for a variety of reasons, either was not in the possession of the FDA (such as items that appeared later in time) or does not appear to have been in the possession of the FDA at the time the NEJM article was published:

1. When reviewing Merck's clinical trials, FDA apparently relied on the pooled Engel analysis and the spreadsheet emailed to the FDA, which both show Merck had 3 pancreatic cancers in the sitagliptin exposed patients and 3 pancreatic cancers in the non-exposed patients. [redacted] See Part X.B.1.a, infra.

2. [redacted]

[redacted] See Part X.B.1.b, infra.

3. [redacted] (discussed directly above), combined with the [redacted] Again, this is information that the FDA would consider relevant when evaluating a CBE regarding pancreatic cancer. See Part X.B.1.c, infra.

4. In response to the FDA's PMR (PostMarketing Requirement), Novo submitted (and published) a study of ZDF rodents, and claimed they found no evidence of proliferation in the ducts. [redacted] See Part X.A.9.b, infra.

5. Shortly after the NEJM article was published, the FDA's Center for Drug Evaluation and Research published two rodent studies involving the administration of incretin mimetics, referred to below as FDA 1 and 2.[65] These two studies confirm a mechanism of injury, proliferation, and dysplasia (abnormal development) consistent with the same type of injury, proliferation, and dysplasia thought to contribute to the initiation and progression of pancreatic cancer in humans. This is information which would support a CBE regarding pancreatic cancer whenever an incretin manufacturer submits one to the FDA. See Part X.A.7, infra.

6. [redacted] information, [redacted] is

[65] The authors of the NEJM article appear to have had access to the FDA 1 results before they submitted the article to NEJM. The FDA 2 results were not submitted for publication until months after the NEJM article was published, so I assume the FDA 2 results were not available when the NEJM article was submitted.

information the FDA would consider highly relevant when evaluating a CBE regarding pancreatic cancer. See Part X.B.5.b, infra.

7. David Madigan, PhD, a professor of Statistics at Columbia University, a past member of the sub-committee of the FDA Science Board charged with reviewing the Center for Drug Evaluation and Research's Pharmacovigilance program, and a current FDA consultant, is serving as another expert witness in this case. He was asked to examine whether a pancreatic signal due to exposure to exenatide, sitagliptin or liraglutide exists in industry standard pharmacovigilance data sources. According to Dr. Madigan's analysis, a clear safety signal has existed since at least as far back as 2011 and as far back as 2008 according to company documents. Dr. Madigan's analysis shows a safety signal for exenatide in the second quarter of 2010, for sitagliptin in the third quarter of 2010, and for liraglutide in the first quarter of 2011. This type of analysis could be done by the incretin manufacturers and is the type of information that the FDA would consider highly relevant when evaluating a CBE. See Part X.B.2.b, infra.

I discuss the above examples in more detail throughout this report. In my opinion, this information is the type of evidence that the FDA would expect to see in a typical CBE submission regarding pancreatic cancer presented for review by the agency. Much of this evidence alone, and particularity when considered as a whole and blended with information already in the FDA's possession, would weigh heavily against the argument that the FDA would have rejected an incretin mimetic manufacturer's CBE regarding pancreatic cancer and would prohibit the manufacturer from adding information about pancreatic cancer.

All of the information, "new" or "old" that could be used to support a CBE regarding pancreatic cancer is discussed below, summarized into the following three general categories:

1. The biological plausibility of the mechanism of the adverse reaction;
2. Evidence of signals that the adverse reaction is occurring, including in either animal or humans; and,
3. The seriousness of the adverse reaction.

A. THE MECHANISM OF ACTION IS BIOLOGICALLY PLAUSIBLE

1. Pancreatic Cancer: Incidence and Origins

Most pancreatic cancer is pancreatic ductal adenocarcinoma, which develops in the exocrine ducts.[66] There are other malignant tumors of the pancreas, including those of the endocrine cells, but they are far less common. When I refer to "pancreatic cancer" here, I mean pancreatic ductal adenocarcinoma unless the context shows otherwise.

Pancreatic cancer occurs at a rate of approximately 12.3 per 100,000 in the general population.[67] In 2014, there will be an estimated 46,420 new cases of pancreatic cancer, with an estimated 39,500 deaths. *Id*. The disease accounts for approximately 6.8% of all cancer deaths, and has a five-year survival rate of only 6.7%. *Id*.

The pancreas is primarily made up of acinar cells (>90%), which produce more than 20 different enzymes.[68] *The Pancreas*, 1168, 1172. Within the islets, beta-cells, which produce insulin, comprise 55% of the cells. *The Pancreas*, 1173. Pancreatic cells have a high degree of plasticity, and "there is increasing evidence that the boundaries that maintain cellular identity can be crossed easily …" *The Pancreas*, 1173. This includes evidence that acinar cells respond to stimuli with "transient changes in cell differentiation state or identity." *The Pancreas*, 1174. Those transformed acinar cells can adopt a beta-cell identity, even producing, processing, and secreting insulin. *The Pancreas*, 1177.

Mice and rats models are often used to study mechanisms in the human pancreas, in part because "human beings and mice … seem to have similar molecular pathways that control cell identity in the pancreas." *The Pancreas*, 1173. Mice models are thus used, for example, to study "the effects on inflammation on the development of pancreatic neoplasia …" *The Pancreas*, 1187. No model, however, is perfect, and each has advantages and disadvantages. *The Pancreas*, 1195. Nonetheless, it is appropriate to rely upon mice and rats models when assessing whether a

---

[66] National Cancer Institute, What You Need To Know About Cancer of the Pancreas. NIH Pub. No. 10-1560, revised May 2010, at p. 1. available online at: http://www.cancer.gov/publications/patient-education/wyntk-pancreas.

[67] SEER Stat Fact Sheets: Pancreas Cancer, available online at: http://seer.cancer.gov/statfacts/html/pancreas.html.

[68] For ease of reference, for this section I have generally cited from a single recent comprehensive reference, rather than a variety of different articles from different times. Most of the materials here are found in May 2013, Vol. 144, Issue 6, "The Pancreas: Biology, Diseases and Therapy," hereinafter, "The Pancreas."

particular pancreatic injury is consistent with the pharmacology of a drug, and the FDA does so itself, and has done so with regard to the specific issue of whether incretin mimetics have the capacity to initiate precancerous changes.

Pancreatic cancer has a genetic component, in the sense that activated Kras, an oncogene, is detected in over 90% of pancreatic adenocarcinomas. *The Pancreas*, 1188. Importantly, however, oncogenic Kras is not, alone, sufficient to transform a cell to make it malignant. *The Pancreas*, 1222. People generally acquire oncogenic mutations in Kras as they age, and numerous studies confirm that healthy people have oncogenic Kras in different organs, including the pancreas, at rates far exceeding the rates of cancer development. *The Pancreas*, 1221–1222. Yet, comparatively few develop pancreatic ductal adenocarcinoma. Thus, the medical community believes that other factors upstream of Kras are necessary for carcinogenesis, for example "epidermal growth factor and inflammation." *The Pancreas*, 1221.

Pancreatic cancer progresses through a series of precursor lesions, the most common of which are known as pancreatic intraepithelial neoplasia ("PanIN"). *The Pancreas*, 1220. Early PanIN lesions will have Kras mutations, but progression also requires inactivation of tumor suppressors, such as p16. *The Pancreas*, 1223. Once the combination of Kras and other factors occurs, progression can be quite swift: in wild-type mice, induction of acute pancreatitis via caerulein "leads to rapid and widespread formation of PanINs," including acinar to ductal metaplasia. *The Pancreas*, 1223. In some models, within 3 weeks of induced damage, "virtually all the ductal structures show characteristics of PanINs." *The Pancreas*, 1223. Over time, the PanINs progress to higher grades, and carcinoma develops. *The Pancreas*, 1223. PanINs are subdivided into PanIN-1A, PanIN-1B, and PanIN-2/3 based on the cytological atypia (structural abnormality) of the duct lining cells, and lesions acquire increasingly higher proliferative potential as they progress towards carcinoma.[69]

The connection between inflammation and pancreatic cancer is well-accepted. "Persistent low-grade inflammation is … an important factor in the development of pancreatic ductal adenocarcinoma." *The Pancreas*, 1199. Chronic pancreatitis increases the risk for pancreatic carcinoma approximately 26-fold.[70] Once chronic pancreatitis has been established, chronic

[69] Koorstra J-BM., et al., Pancreatic Carcinogenesis. J.Pancreatology. 2008; 8:110-125.
[70] Lowenfels, AB., et al., Pancreatitis and the Risk of Pancreatic Cancer. International Pancreatitis Study Group. N.Eng.J.Med. 1993 May 20; 328(20): 1433-1437.

inflammation and enhanced intraductal pressure due to stenosis of the pancreatic duct(s) can lead to the development of pancreatic carcinoma.[71,72] It has been theorized that "inflammatory cells themselves provide signals that promote proliferation of pancreatic epithelial cells that already contain oncogenic mutations." *The Pancreas*, 1175. Further, "inflammation … might accelerate tumorigenesis by causing cells to change their identity, making them more competent to undergo malignant transformation." *The Pancreas*, 1176. Inflammation also "shifts apoptosis-necrosis balance of acing cell death towards necrosis…" *The Pancreas*, 1201. That said, it is not entirely clear how inflammation promotes pancreatic ductal adenocarcinoma initiation and progression, though several mechanisms have been considered, including the facilitation of cancer cell survival and proliferation, the suppression of immunosurveillance, stimulation of the epithelial-mesenchymel transition, amplifying Ras activity, and promoting oncogenic mutagenesis. *The Pancreas*, 1202-1203.

Current research indicates "pancreatic acinar cells can give rise to [pancreatic cancer.]" *The Pancreas*, 1176. [73] As described above, pancreatic cells are prone to changing their state, such as when acinar cells act like beta cells and, in the vulnerable state of de-differentiation, oncogenic stimuli like oncogenic Kras "can divert the regenerative process to initiate neoplastic transformation." *The Pancreas*, 1175. Currently, one of the leading models for the relationship between pancreatitis and pancreatic cancer is a mouse model in which the induction of pancreatitis causes abnormal differentiation of acinar cells which, in turn, produce PanINs, which then progress to higher-grade PanINs and, finally, cancer. *The Pancreas*, 1236.

Summing up the above, as a general matter, pancreatic cells are prone to de-differentiation. Activation of the Kras oncogenic appears a necessary precursor for pancreatic cancer but activation is much more common in the population than pancreatic cancer. Kras activation, therefore is by itself insufficient for carcinogenesis. Inflammation is mechanistically

---

[71] Bhanot, UK., et al., Mechanisms of Parenchymal Injury and Signaling Pathways in Ectatic Ducts of Chronic Pancreatitis: Implications for Pancreatic Carcinogenesis. Lab.Invest. 2009 May; 89(5); 489-497.

[72] Vincent A., et al., Pancreatic Cancer. Lancet. 2011 Aug 13; 378(9791): 607–620.

[73] See also Fokas, E., et al., Pancreatic Ductal Adenocarcinoma: From Genetics to Biology to Radiobiology to Oncoimmunology And All the Way Back to the Clinic. Biochim.Biophys.Acta. 2014 Dec 6; S0304-419X(14)00111- 00115. ("PanIN likely emerges from the Her1-positive stem cell-like cells found at the acini-ductal epithelium junction or the mature acinar cells.").

linked to pancreatic cancer. Acinar cell proliferation may play an important role in pancreatic cancer. Furthermore, and importantly for our purposes, mice and rat models are useful for, and our best means, to study the mechanisms of pancreatic injury. In mice models, an outside stimulus can swiftly produce the initiation or progression of PanINs (which in turn progress to cancer). With an understanding of these basics of pancreatic carcinogenesis, it is *biologically plausible* that an outside stimulus — like a drug that stimulates a proliferative pathway — can produce the initiation or progression of PanINs *in humans* within comparatively short timeframes, i.e., months. [redacted]

2. The Initiation and Progression of Pancreatic Cancer Is Consistent With The Pharmacology of Incretin Mimetics

The theory that the GLP-1 agonists and the DPP-4 inhibitors can initiate or promote the development of pancreatic cancer in humans is consistent with the pharmacology of the drugs.[75] I agree with, and incorporate into my analysis, [redacted]

[74] AMYLN01856403

[75] See Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format (October 2011) p.3, including "the extent to which the adverse event is consistent with the pharmacology of the drug" as a factor for assessing whether there is reasonable evidence of a causal association.

[76] Health Canada Advisement Letter for Januvia. (October 1, 2014), p. 2 (emphasis added MRKJAN0003072602.

3. The FDA Has Repeatedly Shown that It Believes Exocrine and Endocrine Pancreatic Cell Proliferation Is Consistent With the Pharmacology of Incretin Mimetics, and that Pancreatic Cancer Is Consistent with the Pharmacology of Incretin Mimetics

Although I analyze this question independently based upon the available scientific evidence, using the same methodology as an FDA reviewer would, in my opinion such an analysis is redundant: the FDA plainly believes pancreatic cancer is consistent with the pharmacology of the drugs.

If the FDA believed pancreatic cancer was *inconsistent* with the pharmacology of the drugs, it would not have imposed upon the manufacturers a PMR requiring 3-month mice studies in diabetic models with histological evaluation of the exocrine and endocrine pancreas, including ductal structures, as well as assessment of cell proliferation markers in the pancreas. With regard to the latter part, the FDA stated, "To satisfy the PMR, a quantitative evaluation of proliferative markers in the exocrine pancreas, specifically ductal replication/turnover, is required. If an adequate analysis is not possible with existing tissue from the completed study(s), a second study will be required."[77]

If the FDA believed pancreatic cancer was *inconsistent* with the pharmacology of the drugs, it would not have initiated the evaluation referred to in the Public Safety Communication at all. If the FDA performed that evaluation, and concluded pancreatic cancer was *inconsistent* with the pharmacology of the drugs, then it would have reached "a final conclusion … regarding such a causal relationship," but it did not.[78] Finally, if the FDA currently believed pancreatic cancer was *inconsistent* with the pharmacology of the drugs, it would not continue to monitor the situation, such as by evaluating data on pancreatic cancer from clinical trials.

Similarly, if the FDA believed such a link was *inconsistent or implausible*, it would not continue to expend its limited resources performing its own nonclinical research on incretin mimetics to assess "potential mechanisms producing pancreatic injury."[79] The most recent such

[77] Advice Ltr. from U.S. Food and Drug Administration to Merck. (May 17, 2010), MRKJAN0000210840.
[78] Egan, A., et al., Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment. N.Eng.J.Med. 2014 Feb. 27; 370(9): 794-797.
[79] Rouse, R., et al., Extended Exenatide Administration Enhances Lipid Metabolism and Exacerbates Pancreatic Injury in Mice on a High Fat, High Carbohydrate Diet. Plos One. 2014 Oct. 7; 9(1): e109477. Herein, "FDA 2."

research was submitted on June 11, 2014, well after the NEJM article, and published in October 2014. To my knowledge, it reflects the FDA's most recent public activity on pancreatic safety and incretin-based drugs. As explained below, that research further confirmed that incretin mimetic administration has the potential to cause pancreatic injury, including proliferative and atrophic changes of the same sort thought to produce pancreatic cancer in humans.

It is significant that the FDA's own research is showing "The exocrine pancreatic injury induced by [exenatide] and [sitagliptin] in the present study was comparable to the lesions described in experimental acute pancreatitis in Sprague-Dawley rats and C57 mice treated with caerulein, duct ligation, or arginine (Zhang and Rouse, 2013)."[80] As I explained above, in wild-type mice, induction of acute pancreatitis via caerulein "leads to rapid and widespread formation of PanINs," including acinar to ductal metaplasia, and thereafter PanIN formation and progression. *The Pancreas*, 1223. The FDA itself recognized the same in an October 2014 publication, noting "Atrophic changes [induced by exenatide] included proliferative centroacinar cells associated with altered intralobular and main ducts. Similar centroacinar cell proliferation has been proposed as the source of ductal metaplasia that is debated as a precursor to malignant transformation."[81]

Thus, the FDA plainly believes, and has itself independently confirmed, that pancreatic cancer is consistent with the pharmacology of incretin mimetics. The question of whether there is, in fact, a causal relationship is outside the scope of this report because the FDA does not require such a relationship to be proven before a manufacturer may add a risk to the adverse reaction or warnings and precautions sections of a drug's label.

4. The Hallmarks of Cancer

In 2000, Hanahan and Weinberg proposed "six hallmarks of cancer," including sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis.[82] In 2011 they added two "emerging hallmarks," "reprogramming of energy metabolism and evading immune

[80] Rouse R., et al., High Fat Diet and GLP-1 Drugs Induce Pancreatic Injury In Mice. Toxicol.Appl.Pharmacol. 2014 Apr 15, 276(2): 104-114.Herein, "FDA 1."
[81] Rouse, R., et al., Extended Exenatide Administration Enhances Lipid Metabolism and Exacerbates Pancreatic Injury in Mice on a High Fat, High Carbohydrate Diet. Plos One. 2014 Oct. 7; 9(1): e109477. Herein, "FDA 2."
[82] Hanahan, D., and Weinberg, R.A., The Hallmarks of Cancer. Cell. 2000 Jan 7; 100(1): 57–70.

destruction."[83] As noted by Hanahan and Weinberg, arguably the most fundamental trait of cancer cells involves their ability to sustain chronic proliferation. *Id.*

Any substance which triggers sustained proliferative signaling, reduces growth suppressors, resists cell death, reprograms energy metabolism, or reduces immunosurveillance has the potential to be carcinogenic. As shown below, both the natural incretins and their synthetic mimetics have been shown to signal proliferation, resist cell death, and compromise immunosurveillance. I focus here on proliferation, cell death, and indications of dysplasia.[84]

5. Natural Incretins Regulate Cell Proliferation And Survival

GLP-1 and GLP-2 are prototype peptide hormones released from gut endocrine cells in response to nutrient ingestion. Amongst other physiological functions, they also regulate cell proliferation and survival.[85] Beta cell activation of GLP-1 receptor and GIP receptor has been shown to promote insulin secretion, induce beta-cell proliferation, and enhance resistance to apoptosis.[86] Increased insulin production is the desired (and marketed) end-result of GLP-1 mimetic and DPP-4 inhibitor effect upon the pancreas. Indeed, it was the hope of many diabetes researchers that "GLP-1–based therapies would induce pancreatic beta cell regeneration, the Holy Grail of diabetes therapy."[87]

---

[83] Hanahan, D., and Weinberg, RA., Hallmarks of Cancer: The Next Generation. Cell. 2011 Mar 4;144(5): 646-74.

[84] I do not address immune-related issues at length here, but DPP-4 may influence virtually all stages of cancer development and growth, because it participates in regulation of apoptosis, migration, invasion, metastasizing and sensitivity to chemotherapy. Stulc T1, Sedo A., Inhibition of Multifunctional Dipeptidyl Peptidase-IV: Is There a Risk of Oncological and Immunological Adverse Effects? Diabetes.Res.Clin.Pract. 2010 May; 88(2): 125-31. Indeed, within pre- or malignant tissue, DPP-4 seems to have rather antiproliferative and antioncogenic effect and is typically downregulated. Arscott, W.T., Suppression of Neuroblastoma Growth by Dipeptidyl Peptidase IV: Relevance of Chemokine Regulation and Caspase Activation, Oncogene. 2009 Jan 9; 28(4): 479-491.. Thus, it is biologically plausible to expect that inhibition of DPP-4 in the presence of existing pre- or malignant lesions of the pancreas would lead to promotion of these lesions.

[85] Drucker, DJ., Glucagon- Like Peptides: Regulators of Cell Proliferation , Differentiation , and Apoptosis. Molecular Endocrinology 2003; 17(2): 161-171.

[86] Baggio, LL., and Drucker DJ., Biology of Incretins: GLP-1 and GIP. Gastroenterology. 2003 May; 132(6): 2131-2157.

[87] Gale EAM., GLP-1-Based Therapies and the Exocrine Pancreas: More Light, or Just More Heat? Diabetes. 2012 May; 61(5): 986-988.

Consistent with the hallmarks of cancer, Drucker foreshadowed in 2003 that "…the long-term stimulation of cell proliferation, coupled to inhibition of apoptosis, raises theoretical questions about an increased risk of inappropriate cell proliferation and neoplastic transformation in GLP-1R target tissues."[88]

[redacted]

The point here is that because natural incretins regulate proliferation, it is plausible that stimulating the incretin-related pathways will, in turn, stimulate proliferation. A sustained stimulation of proliferation is a hallmark of cancer, perhaps *the primary* hallmark.

[88] Drucker DJ., Glucagon-Like Peptide-1 and the Islet β-Cell: Augmentation of Cell Proliferation and Inhibition of Apoptosis. Endocrinology. 2003 Dec; 144(12): 5145–5148.

[89] [redacted]

[90] [redacted]

[91] LILLY03952854, p. 4.

6. Proliferation and Reduction of Apoptosis, Two Hallmarks of Cancer, in Beta-Cells Is Consistent With The Pharmacology of Incretin Mimetics

A large body of literature has shown that administration of DPP-4 inhibitors and GLP-1 agonists causes the proliferation of beta cells and inhibits beta cell apoptosis in rodents.[92] Although the typical pancreatic cancer in humans does not appear to originate with beta cells, insulinomas are derived from beta cells and they can be malignant, and so the proliferative effect on beta cells shows one mechanism by which incretin mimetics may be potentially carcinogenic.

[redacted] *Id.* at 2. [redacted]

I note that the anti-apoptotic action of GLP-1 on beta cells has also been demonstrated in freshly isolated human islets.[94] Nonetheless, for our purposes here, i.e., whether the FDA would prohibit a warning, it does not matter if the effect has been proven in humans. The FDA's Guidance on Warnings specifically addresses "circumstances in which an adverse reaction that has not been observed with a drug can nonetheless be anticipated to occur," including where "Animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans."[95] Here, the animal data, which consistently show that administration of DPP-4 inhibitors and GLP-1 agonists causes the proliferation of beta cells and inhibits beta cell apoptosis in rodents, would very likely be sufficient to "raise substantial concern about the potential" for carcinogenesis. [redacted]

[92] See Merck's Response to Health Canada's October 1, 2014 Letter (October 30, 2014), MRKJAN0003073635, footnotes 2–9.

[redacted]

[94] Farilla, L., et al., GLP-1 Inhibits Cell Apoptosis and Improves Glucose Responsiveness of Freshly Isolated Human Islets. Endocrinology. 2003 Dec: 144(12): 5149–5158.

[95] Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format (October 2011), p. 5.

[96] AMYLN00039110 at AMYLN00039113.

7. Proliferation in Exocrine Acinar Cells Is Consistent With The Pharmacology of Incretin Mimetics

As discussed above, most of the cells in the exocrine pancreas, including in the ducts, are acinar cells, and there is considerable literature suggesting pancreatic cancer originates with acinar cells. As Gale put it, "GLP-1 receptors are present on other cells [that is, cells other than beta cells] that retain proliferative capacity, thereby raising the possibility that stimulation of these receptors [by incretin mimetics] might promote unwanted proliferation of healthy or abnormal cells in tissues such as the thyroid and exocrine pancreas."[97]

Wistar rats infused with GLP-1 produced cell proliferation in the pancreas and increased pancreatic weight due primarily to increases in proliferative capacity of acinar and duct cells.[98] Nachnani et al studied the effect of exendin-4 (exenatide) on Sprague-Dawley rats and found evidence of inflammation and increased numbers of pyknotic nuclei in the acinar cells.[99]

A study partly supported by Novo Nordisk involving short-term (1 week) administration of exenatide and liraglutide in mice found a rapid increase in pancreatic mass, which the authors acknowledge "cannot be attributed solely to increased β-cell mass."[100] They concluded, among other things, that "GLP-1R [receptor] activation induces a robust induction of gene and protein expression in the exocrine pancreas." The FDA's own researchers later replicated similar results.[101]

Amylin's own research found GLP-1 receptors expressed in acinar cells.[102] If incretins or their mimetics generate a sustained signal for proliferation of acinar cells, then pancreatic cancer

---

[97] Gale EAM., GLP-1-Based Therapies and the Exocrine Pancreas: More Light, or Just More Heat? Diabetes. 2012 May; 61(5): 986-988.

[98] Perfetti, R., et al., Glucagon-Like Peptide-1 Induces Cell Proliferation and Pancreatic - Duodenal Homeobox-1 Expression and Increases Endocrine Cell Mass in the Pancreas of Old, Glucose-Intolerant Rats. Endocrinology. 2000; 141(12): 4600-4605.

[99] Nachnani, JAS., et al., Biochemical and Histological Effects of Exendin-4 (exenatide) on the Rat Pancreas. Diabetologia. 2010 Jan; 53(1):153-159.

[100] Koehler, JA., et al. Glucagon-Like Peptide-1 Receptor Activation Modulates Pancreatitis-Associated Gene Expression But Does Not Modify the Susceptibility to Experimental Pancreatitis in Mice. Diabetes. 2009 Sep; 58(9): 2148-2161.

[101] The second Rouse study described Koehler as: "Similar pancreatic weight findings and pancreatic cell proliferation in response to GLP-1 based therapeutics had been reported in diabetic mice."

[102] Knudsen Deposition p. 280:18-282:16.

would be consistent with their pharmacology. [redacted]

The FDA's own Center for Drug Evaluation and Research has twice confirmed that incretin mimetics can induce suspicious changes in the acinar cells. The first study, done by Rouse (herein, "FDA 1"), found "both [high-fat diet[104]] and GLP-1 drug exposure exacerbated spontaneous changes to acinar cells, inflammation, vascular injury, duct changes, and acinar cell atrophy."[105] FDA 1 further found that the exocrine pancreatic injury induced by exenatide and sitagliptin in the present study was "…comparable to the lesions described in experimental acute pancreatitis in Sprague–Dawley rats and C57 mice treated with caerulein, duct ligation, or arginine."[106] As FDA 2 later recognized as well, FDA 1's histopathological findings are consistent with those described by other authors, including pancreatic inflammation and acinar cell death in EXE-treated Spraque–Dawley rats[107] and necrotizing pancreatitis consisting of acinar cell loss, fibrosis, inflammatory cell infiltrate and ductal metaplasia in a type-2 diabetes rat model.[108] FDA 1 thus recognized exenatide and sitagliptin have the potential to cause a variety of injuries to the pancreas.

The second Rouse study (herein, "FDA 2") found that exenatide for 12 weeks resulted in dose-dependent pancreatic injuries, including "lesions," "frequent acinar cell autophagy," "detectable acinar cell atrophy, ductal hyperplasia, and early fibrosis," as well as "autophagy and mitosis suggestive of proliferation to interstitial fibrosis characterized by proliferating fibroblasts intertwined with injured acinar cells and ductal hyperplasia associated with perivascular

---

[103] *See* e.g. AMYLN 02643315.

[104] The effects of both diet and the GLP-1 based drugs had direct human applicability because (1) high fat and high carbohydrate diets are not uncommon in many human populations and are linked with the development of Type 2 diabetes and (2) the GLP-1 drugs, as discussed, are commonly prescribed for the treatment of Type 2 diabetes.

[105] Rouse, R., et al., High Fat Diet and GLP-1 Drugs Induce Pancreatic Injury In Mice. Toxicol.Appl.Pharmacol. 2014 Apr 15; 276(2): 104-114.

[106] Citing Zhang J. and Rouse RL., Histopathology and pathogenesis of caerulein-, duct ligation-, and arginine-induced acute pancreatitis in Sprague-Dawley rats and C57BL6 mice. Histol.Histopathol. Epub 2014 Mar 3; 29(9): 1135-1152.

[107] Nachnani, JAS., et al.,Biochemical and Histological Effects of Exendin-4 (exenatide) on the Rat Pancreas. Diabetologia. 2010 Jan; 53(1):153-159.

[108] Matveyenko, A.V., et al., Beneficial Endocrine but Adverse Exocrine Effects of Sitagliptin in the Human Islet Amyloid Polypeptide Transgenic Rat Model of Type 2 Diabetes: Interactions with Metformin. Diabetes. 2009 Jul; 58(7); 1605-1615.

inflammatory cells," and further "focal acinar cell necrosis and interstitial inflammation."[109] FDA 2 specifically found "foci of acinar cell autophagy, apoptosis, and necrosis as well as ductal hyperplasia increased with EXE exposure concentrations being most apparent in high dose mice." *Id.* FDA 2 further noted the link between the changes they observed and current leading theories of pancreatic cancer: "Atrophic changes included proliferative centroacinar cells associated with altered intralobular and main ducts. Similar centroacinar cell proliferation has been proposed as the source of ductal metaplasia[110] that is debated as a precursor to malignant transformation." *Id.*

Again, all of the above shows that the FDA's own researchers have now confirmed the very same mechanism I describe here, i.e., that administration of incretin mimetics can induce changes in acinar cells that are of the same type thought to contribute to the initiation and progression of pancreatic cancer in humans.

8. Proliferation in Exocrine Duct Cells Is Consistent With the Pharmacology of Incretin Mimetics

As noted above, GLP-1 receptors are present in many cells that retain proliferative capacity, including duct cells.[111] Gier et al[112] demonstrated that chronic GLP-1 receptor activation stimulated proliferation of 'pancreatic duct glands' or PDGs, which have been identified for their potential role in the pathogenesis of PanIN lesions[113] and, play a role in the development of pancreatic cancer.[114] One of Gier's models was the Kras mouse which, when treated for 12-weeks with exendin-4, showed accelerated disruption of exocrine architecture and

[109] Rouse, R., et al., Extended Exenatide Administration Enhances Lipid Metabolism and Exacerbates Pancreatic Injury in Mice on a High Fat, High Carbohydrate Diet. Plos One. 2014 Oct. 7; 9(1): e109477.
[110] *Id.*, citing Stanger, BZ., Pten Constrains Centroacinar Cell Expansion and Malignant Transformation in the Pancreas. Cancer. Cell 2005 Sep; 8(3) 185-195.
[111] Gale EAM. GLP-1-Based Therapies and the Exocrine Pancreas: More Light, or Just More Heat? Diabetes. 2012 May; 61(5):986-88.
[112] Gier, B., et al., Chronic GLP-1 Receptor Activation by Exendin-4 Induces Expansion of Pancreatic Duct Glands in Rats and Accelerates Formation of Dysplastic Lesions and Chronic Pancreatitis in the Kras(G12D) Mouse Model. Diabetes. 2012 May; 61(5):1250-1262.
[113] Strobel, O., et al. Pancreatic Duct Glands are Distinct Ductal Compartments that React to Chronic Injury and Mediate Shh-induced Metaplasia. Gastroenterology. 2010 Mar; 138(3): 1166-1177.
[114] Bobrowski, A., Risk Factors for Pancreatic Ductal Adenocarcinoma Specifically Stimulate Pancreatic Duct Glands in Mice. Am.J.Pathol. 2013 Mar; 182(3): 965-74.

induced proliferation in the exocrine pancreas. In the rats studied by Gier, marked proliferation of PDGs was observed in relation to formation of PanIN lesions, as was pancreatic weight increases. This study included validation of GLP-1 receptor expression, using immunoflourescent staining.[115]

A 2009 study sponsored in party by Merck compared the effects of sitagliptin and metformin in the HIP rat, a model of Type 2 diabetes. One of the 8 rats exposed to sitagliptin developed severe hemorrhagic pancreatitis. This observation prompted closer examination of the remaining animals, showing increased ductal turnover and ductal metaplasia, a potentially pre-malignant change.[116]

As discussed several times above, both of the Rouse studies by the FDA found evidence consistent with ductal metaplasia. FDA 1 found "duct changes (peri-ductal inflammation and fibrosis)."[117] FDA 2 found "secondary injury in… ducts," including a dose-dependent relationship to ductal hyperplasia that was associated with perivascular inflammatory cells.[118] The authors noted "main pancreatic ductal cell proliferation" as well as "proliferative and atrophic changes … focally in small intercalated ducts with longer term higher doses of [exenatide]." The authors explained:

> **Increased positive Ki-67 immunoreactivity indicated a cell proliferation effect for EXE.** In the Kras ^{G12D} mouse model, EXE increased the number of Ki-67 positive cells in areas of ductal proliferation implying a role for EXE in focal proliferation of the exocrine pancreas and possibly pre-neoplastic PanIn lesion development [28][119]. Recently, increased pancreatic weights and Ki-67 nuclear staining were linked to prolonged GLP-1 based therapy in humans resulting in

[115] Gier, B., et al., Chronic GLP-1 Receptor Activation by Exendin-4 Induces Expansion of Pancreatic Duct Glands in Rats and Accelerates Formation of Dysplastic Lesions and Chronic Pancreatitis in the Kras(G12D) Mouse Model. Diabetes. 2012 May; 61(5):1250-1262.
[116] Matveyenko, A.V., et al., Beneficial Endocrine but Adverse Exocrine Effects of Sitagliptin in the Human Islet Amyloid Polypeptide Transgenic Rat Model of Type 2 Diabetes: Interactions with Metformin. Diabetes. 2009 Jul; 58(7); 1605-1615.
[117] Rouse R., et al., High Fat Diet and GLP-1 Drugs Induce Pancreatic Injury In Mice. Toxicol.Appl.Pharmacol. 2014 Apr 15, 276(2): 104-114.
[118] Rouse, R., et al., Extended Exenatide Administration Enhances Lipid Metabolism and Exacerbates Pancreatic Injury in Mice on a High Fat, High Carbohydrate Diet. Plos One. 2014 Oct. 7; 9(1): e109477., p. 8 "hyperplasia increased with EXE exposure concentrations being most apparent in high dose mice."
[119] Citing Gier, B., et al., Chronic GLP-1 Receptor Activation by Exendin-4 Induces Expansion of Pancreatic Duct Glands in Rats and Accelerates Formation of Dysplastic Lesions and Chronic Pancreatitis in the Kras(G12D) Mouse Model. Diabetes. 2012 May; 61(5):1250-1262.

> unintended pancreatic cell proliferation [5][120]. Similar pancreatic weight findings and pancreatic cell proliferation in response to GLP-1 based therapeutics had been reported in diabetic mice [20][121]. **Consistent with this human data, the present study generated non-clinical evidence of different types of exocrine pancreatic cells (acinar, centroacinar, ductal cells, and even interstitial cells) undergoing proliferation, however, no neoplastic transformation was identified.** In the human study, Ki-67 immunoreactivity was associated with pancreatic intraepithelial neoplasms (PanIN) with exacerbated mucin content within these proliferated cells [5]. In the present study, Ki-67 stained epithelial cell proliferation was observed in main ducts accompanied by expansion of associated mucin-rich goblet cells. These epithelial cells presented as tall columnar cells or pseudostratified epithelial cells in affected areas without morphological evidence of PanIN-like lesions, even though these changes were very similar to illustrations from human studies [29], [30], [5].[122] The mice used in this study were relatively young with no demonstrated predisposition toward development of PanIN-like lesions. **Repetition of this study in mutant Kras mice that develop these lesions may better address the relationship of EXE and pancreatic cancer.[123]**

See FDA 2. Thus, the FDA has found ample evidence that the administration of incretin mimetics can cause ductal cell proliferation in a manner similar to that proposed by Gier and Butler.Further, although FDA 2 did not directly find neoplastic transformation, the FDA plainly believes it is possible that such a neoplastic transformation could occur, and so the authors describe the need for repeating the study in mutant Kras mice, which better replicate the environment of humans with activated Kras. *Id.*

---

[120] Citing Butler, AE., et al., Marked Expansion of Exocrine and Endocrine Pancreas with Incretin Therapy in Human with Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon Producing Neuroendocrine Tumors. Diabetes. 2013 Jul; 62(7): 2595-2604.

[121] Citing Koehler, JA., et al. Glucagon-Like Peptide-1 Receptor Activation Modulates Pancreatitis-Associated Gene Expression But Does Not Modify the Susceptibility to Experimental Pancreatitis in Mice. Diabetes. 2009 Sep; 58(9): 2148-2161.

[122] Citing Hruban, RH., An Illustrated Consensus on the Classification of Pancreatic Intraepithelial Neoplasia and Intraductal Papillary Mucinous Neoplasms. Am.J.Surg.Pathol. 2004 Aug; 28(8): 977-987; Fisher, WE., Pancreas. In Schwartz's Principles of Surgery, 9th ed. Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE, Eds. New York, McGraw-Hill 2009, p. 1167–1243; and Butler, AE., et al. Marked Expansion of Exocrine and Endocrine Pancreas with Incretin Therapy in Human with Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon Producing Neuroendocrine Tumors. Diabetes. 2013 Jul; 62(7): 2595-2604.

[123] Rouse, R., et al., Extended Exenatide Administration Enhances Lipid Metabolism and Exacerbates Pancreatic Injury in Mice on a High Fat, High Carbohydrate Diet. Plos One. 2014 Oct. 7; 9(1): e109477.

9. The Manufacturers Were Told By The FDA To Study How Incretins Could Lead To Pancreatic Cancer

Around the same time that the manufacturers of incretin-based drugs were updating their labels to warn of the risk of pancreatitis, FDA imposed on the manufacturers a Post Marketing Requirement (PMR) that was plainly designed to further investigate a biologically plausible link to pancreatic cancer. Several of these non-clinical studies found evidence that incretin mimetics have the potential to cause pancreatic cancer.[124]

a. Merck's Response to the FDA Post-Marketing Requirement

The FDA informed Merck that four components must be present for the PMR to be satisfied: (1) Use of diabetic models, marked by high blood glucose/triglycerides; (2) At least 3 months duration of dosing with Sitagliptin; (3) Histological evaluation of the exocrine and endocrine pancreas, including ductal structures; and (4) Assessment of cell proliferation markers (e.g. BrdU, KI67, PCNA) in pancreas. With regard to number four the FDA stated, "To satisfy the PMR, a quantitative evaluation of proliferative markers in the exocrine pancreas, specifically ductal replication/turnover, is required. If an adequate analysis is not possible with existing tissue from the completed study(s), a second study will be required."[125]

Merck made several efforts to avoid complying with the PMR.

i. The Mu Study

Initially, Merck attempted to submit a study that it had already completed, known as the "Mu study." The Mu study was published as Mu et al., Eu. J. Pharm. 2009, Vol 623:148-154.[126] The Mu study stated that the improved β cell mass was likely due to reduced apoptosis rather than increased proliferation. *Id.* Merck submitted this data to FDA on December 21, 2009.[127] The

[124] Ltrs. From U.S. Food and Drug Administration to Merck, Amylin, and Novo Nordisk. MRKJAN0000210624 (October 16,2009), AMYLN02821497 (October 30, 2009), NNI-NDA-22341-00000103 (January 25, 2010).
[125] Advice Ltr. From U.S. Food and Drug Administration to Merck. (May 17, 2010), MRKJAN0000210840.
[126] Mu, J., et al., Inhibition of DPP-4 with Sitagliptin Improves Glycemic Control and Restores Islet Cell. Mass and Function in a Rodent Model of Type 2 Diabetes. Eur.J.Pharmacol. 2009 Nov 25; 623(1-3): 148-154.
[127] Submission from Merck to U.S. Food and Drug Administration. (December 21, 2009), MRKJAN0000195780 and MRKJAN0000195786.

FDA questioned whether the Mu study met the PMR requirements.[128] On July 6, 2010 Merck responded to the FDA's request, but did not respond to the fourth requirement of the PMR regarding an analysis of quantitative proliferation in the exocrine pancreas and ductal replication/turnover.[129] [redacted] On September 22, 2010 the FDA informed Merck that it was unlikely the Mu study would satisfy the PMR based on the lack of adequate drug exposure.[131] On September 24, 2010 the FDA reminded Merck to submit a new protocol and on November 8, 2010 Merck informed the FDA they had an ongoing second preclinical pancreatic safety study and expected to have data by the end of 2010.[132]

ii. The Hull Study

After the rejection of Mu, Merck also tried to satisfy the PMR by altering an on-going study unrelated to pancreatic safety.[133] [redacted][134] On March 25, 2011 Merck provided FDA with some initial information about this study but did not include a full protocol.[135] In June of 2011 Merck told FDA that the study would now be

[128] Advice Ltr. from U.S. Food and Drug Administration to Merck. (May 17, 2010), MRKJAN0000210840.
[129] Submission from Merck to U.S. Food and Drug Administration. (July 6, 2010), MRKJAN0000202030, MRKJAN0000202036, and MRKJAN0000202048.
[130] MRKJAN10000341652.
[131] Advice Ltr. From U.S. Food and Drug Administration to Merck. (September 22, 2010), MRKJAN0000210872.
[132] Warning Ltr. from U.S. Food and Drug Administration to Merck. (February 17, 2012), available online at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm293490.htm.
[133] *Id*., and MRKJAN10000259303; [redacted] MRKJAN10000281238.
[134] MRKJAN10000259303, MRKJAN0000205042, and MRKJAN 10000930779.
[135] Supplement NDA 21-995 Proposed REMS Modification. MRKJAN0000204214 and MRKJAN0000204223.

completed by August 2011, not June 2011, as it had told FDA previously.[136] FDA responded that they were concerned that the study might not satisfy the PMR since no protocol had been submitted. *Id.*

On November 7, 2011 FDA issued a *Failure to Respond Letter* to Merck for its failure to satisfy the PMR, because Merck had still not submitted the Kahn and Hull study that it had first promised to deliver by June of 2011.[137] Merck responded on November 21, 2011, but failed to acknowledge the FDA had not agreed the ongoing independent study could be used to satisfy the PMR.[138] [redacted].[139] The FDA determined that Merck had not shown good cause for failing to adhere to the agreed timetable for PMR completion on November 30, 2011.[140] Merck submitted additional data from the Kahn and Hull study on January 6, 2012 but the FDA did not consider this submission a final report and informed Merck there was still insufficient information to evaluation the study. *Id.*

[redacted]

[136] Warning Ltr. from U.S. Food and Drug Administration to Merck. (February 17, 2012), available online at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm293490.htm.
[137] Failure to Respond Ltr. from U.S. Food and Drug Administration to Merck. (November 7, 2011), MRKJAN0000575251.
[138] Warning Ltr. from U.S. Food and Drug Administration to Merck. (February 17, 2012), available online at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm293490.htm.
[139] MRKJAN0000205026.
[140] Warning Ltr. from U.S. Food and Drug Administration to Merck. (February 17, 2012), available online at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm293490.htm.
[141] Merck Submission to U.S. Food and Drug Administration. (February 9, 2012), MRKJAN0000017403.

[redacted][142] This statement in the final publication is wrong [redacted][143]

iii. The Forest Study

After the FDA did not accept the Hull and Mu studies as satisfying the PMR, Merck conducted an internal study using a Zucker Diabetic Fatty (ZDF) rat model [redacted]"[144] It is concerning that in the study, Sitagliptin had no impact on blood glucose in the ZDF rats.[145] [redacted][146] Nonetheless, Merck presented these results on ductal proliferation both to the public and to the FDA. The limitations of the Merck ZDF study call into serious question any conclusions drawn therefrom.

b. Novo's Response to the FDA Post-Marketing Requirement

Novo responded to the FDA's PMR with its own 13-week study of ZDF rats, the results of which were eventually published.[147] The study first conceded an important point, i.e., "Preclinical studies have indicated the presence of a functional GLP-1 receptor on acinar cells (15, 26, 32, 34) and on pancreatic ductal cells (44, 45)." (Citations to research omitted here.) As described above, if acinar cells or ductal cells have GLP-1 receptors, then they have the potential

[142] Aston-Mourney, K., et al., One Year of Sitagliptin Treatment Protects Against Islet Amyloid-Associated β-cell Loss and Does Not Induce Pancreatitis or Pancreatic Neoplasia in Mice. Am.J.Physiol.Endocrinol.Metab. 2013 Aug 15; 305(4): 475-484.
[143] MRKJAN10000803485.
[144] MRKJAN0000195786.
[145] Three-Month Oral Study in Zucker Diabetic Fatty (ZDF) Rats MRKJAN0000365495.
[146] Knudsen Deposition p. 134:6 – 137:11.
[147] Vrang, et al., The Effects of 13 Wk of Liraglutide Treatment on Endocrine and Exocrine Pancreas in Male and Female ZDF Rats: A Quantitative and Qualitative Analysis Revealing No Evidence of Drug-induced Pancreatitis. Am.J.Physiol.Endocrinol. 2012 Jul 15; 303(2): 253-264.

to receive a sustained proliferative signal from incretin mimetics, which makes carcinogenesis consistent with their pharmacology.

Novo claimed in the study that "qualitative histopathological findings did not reveal adverse effects of liraglutide" in the pancreas, that there were "no effects of liraglutide or exenatide on overall pancreas weight or exocrine and duct cell mass or proliferation," and that "no effect on the exocrine pancreas" was detected. *Id.* The study specifically referenced the work of Matveyenko and Gier, and indicated it had failed to replicate those findings, although the study conceded "because the mass of the collecting ducts (including the periductal glands that also express CK20) makes up only a fraction of total duct cell mass, we cannot exclude a potentially increased proliferation in this particular cell type." *Id.*

In fact, Novo's study actually *confirmed* the findings of Matveyenko and Gier, as explained below.

[redacted]

As explained above, growth in the ducts would indicate that proliferation, and thus carcinogenesis, is consistent with the pharmacology of the drugs. [redacted]

[148] NOVO-02278271 and NOVO-02348487.
[149] NOVO-02278271, p. 14.
[150] NOVO-02348487, p. 8.
[151] Knudsen Deposition, p.159:19 -160:6: [redacted]

B. THERE IS SUBSTANTIAL EVIDENCE THAT THE ADVERSE REACTION OF PANCREATIC CANCER IS OCCURRING IN HUMANS EXPOSED TO INCRETIN MIMETICS

I have discussed above the biologic plausibility for incretin mimetics causing pancreatic cancer. Plausibility is the first consideration for determining both the obligation of the manufacturer to initiate a CBE and the likelihood that FDA would accept a CBE. I now turn to the second consideration for CBE submission, i.e., the strength of the evidence from patients on incretin therapies. I will explain in detail why the strength of evidence is more than enough to justify the submission and acceptance of a CBE. I will also discuss why the threshold for informing prescribers of potential drug-induced serious adverse effects is much lower than that for estimating the safety profile in the New Drug Application review process.

1. The Manufacturers' Clinical Trials

a. Merck's Clinical Trial Data

Merck is in possession of relevant information arising out of its clinical trials. That information is not in the FDA's possession, and could have been submitted by Merck to support a CBE regarding pancreatic cancer.

Merck has published three pooled analyses of the clinical trials sponsored and funded by Merck. These publications are based on "Integrated Summary of Safety" reports, which are generated to summarize the adverse events across clinical trials. The first two pooled analysis are not relevant here, in that Merck did not specifically analyze adverse event data for pancreatic cancer. However, Merck specifically analyzed adverse event data for pancreatic cancer in the third pooled analysis, "Safety and Tolerability of Sitagliptin in Type 2 Diabetes: Pooled Analysis of 25 Clinical Studies" published May 23, 2013.[152]Specifically, Merck wrote: "The exposure-adjusted incidence rates for the pooled terms related to the category of pancreatic cancer were similar in the two treatment groups (0.05 and 0.06 events per 100 patient-years in the sitagliptin and nonexposed groups, respectively)." Merck did not publish the raw numbers of pancreatic cancer in the treatment and comparator groups.

[redacted]

[152] Engel, S., et al. Safety and Tolerability of Sitagliptin in Type 2 Diabetes: Pooled Analysis of 25 Clinical Studies. Diabetes.Ther. Jun 2013; 4(1): 119-145.

At the National Institutes of Health (NIH) meeting held in June of 2013, Merck employee Sam Engel presented the raw numbers from the pooled analysis. Mr. Engel represented that there were 3 pancreatic cancer adverse events out of 7,726 patient years in the Sitagliptin group and 3 pancreatic cancer adverse events out of 6,885 patient years in the non-exposed group.[153]

However, the protocol and statistical analysis plan for the 2013 pooled analysis excluded patients in studies conducted exclusively in renally-impaired patients and studies conducted in Japan.[154] Patients in these studies were administered doses lower than the standard 100 mg dose. *Id*. [redacted].[155] There is no justification for excluding those cases from the pooled analysis. As a result of their smaller body weights, Japanese patients typically experience the same or greater systemic exposure to drugs with smaller or similar doses to Western patients. Japanese patients are often therefore the sentinel population for a safety issue. We found this at FDA when we reviewed and later approved acarbose, another Type 2 diabetes therapy. We received a number of reports of hepatic injury in small Japanese women. This led to a reduction in the approved dose range for acarbose. The same principle applies to renally-impaired patients. These patients will typically have exposures that are comparable to non-impaired patients even when taking lower doses. It is permissible by standard analytical principles to report several different analyses by subgroups. It is never permissible to exclude a particular subgroup without explicit, clearly stated justification.

If the patients from the renally-impaired and Japanese were included in the pooled analysis, [redacted] These findings are relevant and an important consideration relative to the risk of pancreatic cancer.

By peer convention, the total pancreatic cancer numbers should have been included in the publication, the NIH presentation and, as discussed below, highlighted to the regulatory and

[153] Clinical Data on Pancreatitis and Pancreatic Cancer in Studies with Sitagliptin. MRKJAN10000183562.
[154] Integrated Statistical Analysis Plan MK-0431 Integrated Summary of Safety. MRKJAN10000239605.
[155] Engel Deposition p. 173:12-179:21, MRKJAN0001368811, MRKJAN0001368786, MRKJAN0001368761.

medical community, both of which were seeking information on pancreatic cancer in clinical trials.

The NEJM article specifically cites the clinical data in Engel et. al., [redacted]

Additionally the NEJM article stated, "Clinical safety databases reviewed by the FDA included data from more than 200 trials, involving approximately 41,000 participants, more than 28,000 of whom were exposed to an incretin-based drug; 15,000 were exposed to drug for 24 weeks or more, and 8500 were exposed for 52 weeks or more." [redacted]

Based upon my experience, [redacted] is information the FDA would consider relevant when evaluating a CBE regarding pancreatic cancer.

[156] MRKJAN10000476895.
[157] MRKJAN10000464173 and MRKJAN10000464175.

b. Novo Clinical Trial Data

Novo is in possession of relevant information arising out of its clinical trials. That information is not in the FDA's possession, and could have been submitted by Novo to support a CBE regarding pancreatic cancer.

In Novo's Annual Review submitted August 23, 2013 for Victoza (the most current annual review document available to the Plaintiffs in Novo Nordisk's production), [redacted]

[redacted][159]

Novo recently applied for another indication for liraglutide. However, in the new indication, it has the commercial name of "Saxenda" instead of "Victoza" and would allow liraglutide to be used in the treatment of obesity. Since the development program is separate from Victoza, (the diabetes indication), Novo Nordisk did not have to report any pancreatic cancers that were detected in the liraglutide treatment group. [redacted] is unlikely that this information was considered by FDA in relation to Victoza. [redacted] which the FDA would consider relevant when evaluating a CBE regarding pancreatic cancer, and it would have weighed against the FDA rejecting the CBE and prohibiting the warning.

[158] Addendum to Clinical Overview. NOVO-00948679.

[159] [redacted]. (NOVO-00118902 at p. 40 and NOVO-00264339 at p. 171). I similarly do not include it in my analysis.

[160] NOVO-01518117.

c. Merck, Novo and Amylin/Lilly Clinical Trial Data Combined

[redacted] is information which the FDA would consider supportive of a CBE regarding pancreatic cancer.

In my opinion, if I back at FDA and responsible for DMEP at the time, and based on regulatory and scientific practice I would have considered the results of meta-analyses of clinical trials suggesting the potential for pancreatic cancer risk important and necessary for physicians to know in deciding when to prescribe incretins or not.

2. <u>Post-Marketing Surveillance</u>

a. Overview of Adverse Event Reporting ("AERs")

Premarket safety studies cannot detect all of the potential adverse effects related to a drug because the testing is conducted with limited numbers of patients and because the types of patients are more diverse in market experience than in clinical trials. As both a matter of regulation and as a matter of industry practice, manufacturers are required to continue to collect and report adverse experience information after drug approval.

This postmarket surveillance includes spontaneous reports of individual cases from health care practitioners, patients, and others, foreign adverse experience reports, new clinical trials, information from the medical literature and other available databases, such as FDA's Adverse Event Reporting System (FAERS).

A manufacturer has a continuing obligation to update its label based on newly acquired information, including spontaneous reports of adverse events. Again, this makes sense as described in FDA's *Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, which states the following in section III:

> Risk assessment during product development should be conducted in a thorough and rigorous manner; however, **it is impossible to identify all safety concerns during clinical trials.** Once a product is marketed, there is generally a large

[161] AMYLN05123059.

> increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, **post-marketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.** (Emphasis added).[162]

Spontaneous postmarketing adverse event reports must identify at least: 1) the adverse event(s); 2) possible suspect drug(s); 3) a specific patient; and 4) the source of the report.[163] There are limitations to spontaneous reports which must be taken into account. For example, patients may have multiple medical problems, they may have taken many different medications, and the reports often have incomplete information and lack follow-up information.

FDA specifies in its regulations when and how to report adverse events, with a particular focus on reporting "serious" and "unexpected" events, terms defined by FDA regulations. These events are to be reported to the FDA within 15 days of receipt by the manufacturer. The FDA adverse event report database, FAERS (formerly AERS and before that SRS) is available to the public. The coded sections of the reports are available quarterly for download.

An important purpose of spontaneous reporting systems is to detect a "signal" of a previously unknown potential association between an adverse effect and a drug. Beyond examining individual spontaneous reports, signal evaluation may include epidemiological studies, research on the pathophysiology of the adverse reaction and, where feasible, clinical trials.

The separate report of Dr. David Madigan, discussed below, addresses issues of emergent signals for pancreatic cancer in the FAERS and the refinement of those signals.

b. ***Analysis Of The FAERs Database Shows A Signal Of Disproportionate Reporting Of Pancreatic Cancer For Each Of The Incretin-Based Therapies***

[redacted]

[redacted]

[162] Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 22, 2005).

[163] Gliklich, RE., et al., Registries for Evaluating Patient Outcomes: A User's Guide [Internet]. 3rd edition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. 12, Adverse Event Detection, Processing, and Reporting, available online at: http://www.ncbi.nlm.nih.gov/books/NBK208615/.

[redacted][165].

FDA's Jonathan Levine, in a September 2005 discussion of disproportionality analysis to systematically and simultaneously detect safety signals in AERS, concluded:

- "AERS provides useful information about adverse events.
- Clinical trials cannot replace the information provided by AERS.
- Biases exist in AERS, and the exact nature of the biases is impossible to determine.
- Disproportionality analysis can provide an understanding of the associations between drug-event pairs in AERS.
- Disproportionality analysis of AERS cannot by itself determine if there is a causal link between a drug-event pair."[166]

The most conservative threshold for when a drug-event combination is considered an SDR is when the EB05 ≥ 2.[167] A drug company can, and in many circumstances *should* or *must* use less conservative thresholds, but I do not address in this report those issues. Rather, the EB05 is useful here because it can show us how, even under the most conservative analysis used in the field, there were signals, before the NEJM article and after, that would support a CBE.

As part of my preparation for this report, I reviewed David Madigan, PhD's report in this matter. Dr. Madigan's credentials are in his report; he is well-qualified to opine on this matter, and the FDA in the past has turned to him for his expertise in this very field. As part of his report

[164] AMYLN00240832.
[165] Yu Deposition p. 141:4 – 141:17 and MRKJAN0000555403.
[166] Available online at: http://www.amstat.org/meetings/fdaworkshop/presentations/2005/P01_Levine%20PostMarketing%20Surveillance.ppt, last accessed on December 2, 2014.
[167] According to the FDA, the EBGM (Empirical Bayes Geometric Mean) is an adjusted ratio of the number of the number of observed incidences to the number of expected incidences in a database. For example, "if EBGM=3.9" for a drug-event combination, "then this drug-event combination occurred in the data 3.9 times more frequently than expected." EB05 is the "estimated lower 95% 'confidence limit' for the EBGM." So, "if EB05=20, then the drug-event occurred AT LEAST 20 times more frequently in AERS than expected." For the "Data Mining Signal ('Threshold Interval') EB05>=2," the "drug-event occurred AT LEAST twice as often as expected. This threshold gives assurance that potential safety signals are unlikely to be noise." See http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm080547.ppt [Emphasis in original]

Dr, Madigan ran reports of the AERs using the EB05 metric. The information below was taken from the "Results" section of his report, with the exception of the footnotes, which are omitted here:

> 35. Here I report my analysis of AERS using the EB05 metric. EB05 is more conservative than EBGM, PRR or ROR and as such, any signal flagged by EB05 would certainly generate a signal using the other metrics. Figure 1 shows the EB05 values over time for the pancreatic cancer. I provide the underlying numerical results for EB05 and other metrics for each figure in an Excel spreadsheet.

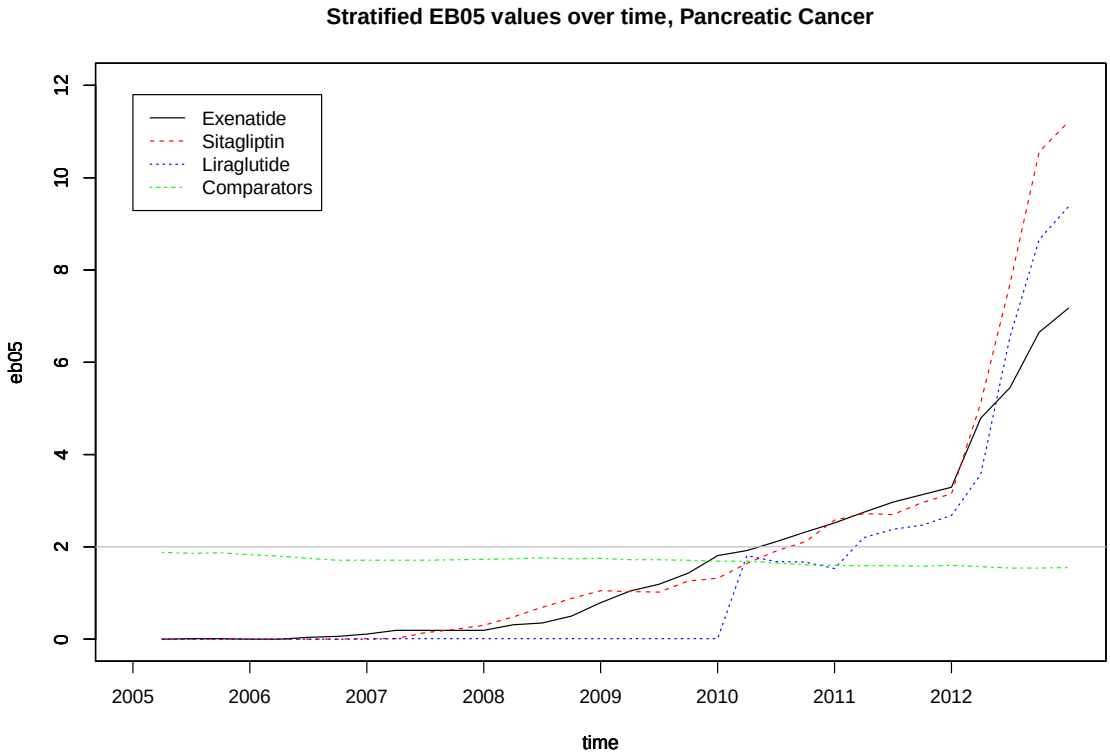


Figure 1. Stratified EB05 analysis for the pancreatic cancer for GLP-1 agents and the comparators.

> 36. Using the conventional threshold of 2, Figure 1 shows that the GLP-1 agents generated a signal for pancreatic cancer as early as 2010. The comparators never reach the signaling threshold.

> 37. Table 1 provides estimated effect sizes using regularized logistic regression. These are on the scale of odds ratios so that an estimate of one represents no effect while an estimate of, for example, 6.17 for Exenatide as of the end of 2012 represent a more than six fold increase in the odds of pancreatic cancer, adjusting for age, sex, year of report, *and all other drugs*. Using a threshold of 2, i.e. a doubling, all three GLP-1 agents show a safety signal as early as the end of 2010.

Table 1. Exponentiated regularized logistic regression coefficients for GP-1 agents and comparators for developmental delay. Logistic regression fit using the CCD software with a prior variance of 0.1.

	Year Ending				
	2008	**2009**	**2010**	**2011**	**2012**
Exenatide	1.12	2.16	2.92	3.69	6.17
Sitagliptin	1.53	1.85	3.06	3.42	6.69
Liraglutide	n/a	n/a	2.08	4.03	7.51
Comparator	1.98	1.90	1.82	1.79	1.64

Dr. Madigan also performed sensitivity analyses, in which the suspect-only and serious-only analyses yield stronger signals. The FDA would consider those important as well in evaluating a CBE, but I need not address them in depth because the basic analysis already provides a signal.

As indicated in the above tables, the EB05 score was greater than 2 for each drug when compared against all drugs in the FDA-AERS database. Accordingly, there was and remains a signal of disproportionate reporting with **24 diabetes drug controls**[168] when compared to all drugs in the FDA-AERS database. In his conclusion, Dr. Madigan states the following:

> Evidence that exposure to GLP-1 agents could cause pancreatic cancer has existed for many years. Against that backdrop, routine analyses of spontaneous reports show a clear safety signal has existed since at least as far back as 2011 and as far back as 2008 according to company documents. My analysis shows a safety signal for exenatide in the second quarter of 2010, for sitagliptin in the third quarter of 2010, and for liraglutide in the first quarter of 2011. No such signal arises for other anti-diabetic agents.

In my opinion, the Signal of Disproportionate Reporting regarding pancreatic cancer in the FDA-AERS database would be significant to the FDA, and supportive of submission of a CBE regarding pancreatic cancer. In my opinion, if I were back at FDA and responsible for

[168] Avandia, rosiglitazone, glucotrol, amatyl, diabeta, euglucan, glynase, micronase, cetohexamide, arbutamide, hlorpropamide, lipizide, liclazide, libenclamide, lyburide, libornuride, liquidone, lisoxepide, lyclopyramide, limepiride, olazamide, olbutamide, metformin and glucophage.

DMEP at the time, and based on regulatory and scientific practice, I would have considered the body of SDR evidence suggesting the potential for pancreatic cancer risk important and necessary for physicians to know in deciding when to prescribe incretins or not.

In my opinion, based on my experience and regulatory standards, the Signal of Disproportionate Reporting result for incretins and pancreatic cancer compared to all drugs in the FDA-AERS database, even under this most conservative of analyses,[169] is sufficient evidence of a causal association between the incretins and pancreatic cancer to provide this information to the medical community, potential prescribing physicians, and patients. In my opinion, such evidence would support a reference to pancreatic cancer in each of the incretin labels. In my opinion, as an endocrinologist and former senior regulatory official, it would have been important to me that such a reference to pancreatic cancer be included in the incretin labels. In my opinion, an appropriate statement in the label about pancreatic cancer risk has been needed since the availability of the data discussed immediately above to allow a prescribing physician to make an informed decision about whether the benefit to risk relationship for treating an individual patient with an incretin drug is either favorable or not.

3. Epidemiology: Scientific Literature

Epidemiological studies (ES) also support the submission of a CBE which adds risk information about pancreatic cancer to the labels of the incretin medications. Epidemiologic studies differ from well controlled clinical studies in that the former are typically done with data that were generated before the study was designed. These studies also do not allow for randomization, another important measure for reducing bias in analyzing and interpreting data. ES nonetheless are the most important means of evaluating risks in the marketing phase, short of well-controlled clinical trials, which are very costly, time consuming, and difficult to adequately power from a statistical standpoint. Hereto, the evidence provided by ES is in itself sufficient to justify the submission and acceptance of a CBE for pancreatic cancer risk.

[169] Again, I do not address here what a reasonable drug manufacturer should have done. In many circumstances, potentially including this circumstance, an EB05>2 is too conservative a metric to assess whether a reasonable drug manufacture would assess a safety signal based on AERs even sooner. I use it here for purposes of this preemption analysis only.

a. Article – Elashoff M., et al., Pancreatitis, Pancreatic, and Thyroid Cancer With Glucagon-Like Peptide-1-Based Therapies. Gastroenterology, 141:150-156, 2011

Elashoff examined the FDA adverse events reporting database from 2004 to 2009 for reports associated with the GLP-1 agonist exenatide (Byetta) and the DPP-4 inhibitor sitagliptin (Januvia). The authors found statistically significant reported event rates for pancreatic cancer that were 2.9 times greater for exenatide and 2.7 times greater for sitagliptin, as compared to other therapies. [170]

b. Article – Institute for Safe Medicine Practices, Perspectives on GLP-1 Agents for Diabetes. QuarterWatch, April 18, 2013

QuarterWatch is a publication that monitors serious adverse drug events reported to the FDA. This article analyzed adverse event reports from July 1, 2011 through June 30, 2012 for five incretin mimetics: Byetta, Victoza, Januvia, Onglyza and Tradjenta.[171] These were compared against three sulfonylurea drugs (glipizide, glimepiride and glyburide) and metformin, the most widely used oral medication for diabetes. A safety signal for pancreatic cancer was found for the incretin mimetics, with a statistically significant odds ratio of 25.6 (95% CI 15.9-47.8). This is indicative of a 24,600 percent increased risk. *Id*. at 2.

The QuarterWatch results are consistent with the findings of Elashoff, published two years earlier. It is noteworthy that there was no overlap in the dates of the adverse events studied by Elashoff (2004-2009) and QuarterWatch (2011-2012). In my experience, the consistency of results over time will be significant to FDA when reviewing a CBE that adds risk information to a drug's label. Also, Byetta was approved in 2005 and Januvia in 2006, so those drugs had only recently come to market when data was gathered for the Elashoff study. Byetta and Januvia had been on the market for approximately five years by the time they were evaluated by the researchers at QuarterWatch. This suggests that Elashoff's results were not an anomaly caused by the relatively brief time the drugs had been on the market, which again will be favorably considered by the FDA when reviewing a pancreatic cancer CBE.

---

[170] Elashoff, M., et al., Pancreatitis, Pancreatic, and Thyroid Cancer with Glucagon-like Peptide-1-based Therapies. Gastroenterology. 2011 Jul; 141(1): 150-156.

[171] Institute for Safe Medicine Practices, Perspectives on GLP-1 Agents for Diabetes. QuarterWatch, April 18, 2013, available online at: http://www.ismp.org/quarterwatch/pdfs/2012Q3.pdf.

A possible explanation for the observed increase in risk of these drugs during the years examined by QuarterWatch is the so-called "Weber effect." This was first reported in 1984, describing adverse event reporting trends in the United Kingdom for oral non-steroidal anti-inflammatory drugs (NSAIDs).[172] The Weber effect was "often too simply summarized as 'after regulatory approval of a drug, AE reporting increases over the first 2 years, peaks near the end of year 2, and then reliably, and rapidly, diminishes with further time on the market.'"[173] Subsequent studies have shown that the Weber effect has questionable validity, if any.[174] In addition, the years covered by the QuarterWatch study extend well beyond the 2-year time frame posited by Weber. Based on my experience, it is my opinion that if these studies are used in support of a CBE, the FDA will not deem any of them irrelevant because of the "Weber effect."

c. Article – Nauck M., Friedrich, N., Do GLP-1-Based Therapies Increase Cancer Risk? Diabetes Care, Vol. 36 (Supp. 2), August 2013

Nauck sought to replicate the Elashoff study using a broader set of search terms and additional adverse event reports that had become available in the interim (events from 2nd quarter 2005 through 2010).[175] The study "confirmed a significantly elevated odds ratio for pancreatitis and pancreatic cancer with both exenatide and sitagliptin," and noted that further studies would help to more fully assess the risks. *Id.* at S249-51.

4. <u>Epidemiology: The Manufacturers' Studies</u>

Of all the epidemiologic studies performed by the manufacturers, some of suggest an association between the use of incretin medications and pancreatic cancer and some do not. It is

[172] Weber, J. Epidemiology of Adverse Reactions to Nonsteroidal Anti-inflammatory Drugs. Adv.Inflamm.Res. 1984; 6:1–7.

[173] Hoffman, KB., et al., The Weber Effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): Analysis of Sixty-Two Drugs Approved from 2006 to 2010. Drug.Saf. 2014 Apr; 37(4):283-294.

[174] *See* Chhabra, P.,et.al., Adverse Event Reporting Patterns of Newly Approved Drugs in the USA in 2006: An Analysis of FDA Adverse Event Reporting System Data. Drug.Saf. 2013 Nov; 36(11):1117-1123.(results of study did "…not support the existence of the Weber effect in contemporary AE reporting in the USA (and,) on the contrary, no one pattern of AE reporting predominated."); Hoffman, KB., et al., The Weber Effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): Analysis of Sixty-Two Drugs Approved from 2006 to 2010. Drug.Saf. 2014 Apr; 37(4):283-294.(Weber effect should not be assumed when analyzing modern-day FAERS reporting).

[175] Nauck M., and Friedrich, N., Do GLP-1-Based Therapies Increase Cancer Risk? Diabetes Care, Aug 2013; 36(2): 245-252.

my opinion that those studies that did not suggest an association lack sufficient statistical power to meaningfully address the risk of pancreatic cancer related to the incretin mimetic drugs. In these cases, absence of evidence is not evidence of absence. As part of my experience and training, and part of my work at FDA, I have been routinely required to assess the meaning of various study results from a statistical perspective. Although I interpret such results, I do not possess the skills and knowledge to compute these results and I rely on the expertise of others to perform statistical calculations. Such reliance is routine among experts in my field. The information we require is typically provided within a journal article or data summary in a regulatory submission.[176] Low statistical power is an important limitation with all of the epidemiological studies done by the incretin manufacturers.

The problem of insufficient statistical power has been recognized by the manufacturers as well. [redacted]

While FDA will review all studies and other information submitted in connection with a CBE, it has been my experience and is my opinion that the agency will not refuse to allow a manufacturer to add risk information to a label simply because there are no clearly statistically significant findings from epidemiological studies to support that risk information. It takes time to obtain statistically significant study results. That is one of the reasons that FDA, both in practice

[176] I also rely in part on the definition of statistical power available on The Oxford University medical website "Bandolier." That definition states that statistical power is "The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists…. If the statistical power of a study IS low, the study results will be questionable (the study might have been too small to detect any differences)." available online at:
http://www.medicine.ox.ac.uk/bandolier/booth/glossary/statpow.html).
[177] Buse Deposition p. 200:12 – 201:20.
[178] Buse Deposition p. 198:22 – 203:8.

and as expressed in its regulations and guidance documents, does not require that causal relationships be fully established before risk information be provided to prescribers and patients.

a. Byetta's Epidemiological Studies

There are two studies at issue for Byetta: Aperio and Optum. My review causes me to dismiss Aperio as unreliable. While the Optum study suggests an increased pancreatic risk, it also suffers from many of the same weaknesses as the Aperio study, and cannot be relied on to prove (or disprove) an increased risk.

i. Byetta Aperio Study

Aperio was a signal detection tool that was used to evaluate the existence of signals for pancreatic cancer in a health insurance database.[179] [redacted] The study is not useful for answering questions about the relationship between Byetta and pancreatic cancer.

[redacted]

[179]AMYLN05137689 at AMYLN05137690.
[180]LILLY05382098.
[181]LILLY01427987.
[182]LILLY01426777.
[183] MRKJAN10000314459.
[184] *Id*. at MRKJAN10000314465.
[185] AMYLN05278007 at AMYLN05278010.

[redacted] To understand the how an ES is interpreted by FDA, it is very important to recall the definition of 'statistical significance" (SS). The long held convention of FDA and biologic scientists in general is that SS is defined if the probability of a result occurring purely by chance is equal to or less that 5% (indicated by $p \leq .05$). If the p value for the primary endpoint of a clinical study is .06, the trial would be considered to have failed to show the hoped for result. This illustrates that the definition of clinical significance is purely arbitrary. The difference between .05 and .06 is mathematically negligible but it represents a huge difference in evaluating efficacy by FDA. On the other hand, at FDA, safety evaluation, whether it be of well controlled studies or ES, has an entirely different standard. Reviewers would generally regard a p value of .10 or even .20 for an adverse event as reflecting a signal that at least should be considered and documented, if not pursued. In other words, in the review of safety data, FDA seizes on signals (also called trends) which have substantially greater probabilities of being related to chance. This is reflects a conservative approach for evaluating safety data, which are almost always available in limited supply.

b. Merck's Epidemiological/Observational Studies

There are three studies at issue for Merck. Due to their limitations, they offer little, if any, "evidence of absence" on the long term risk of developing pancreatic cancer associated with Januvia.

[186] *Id.* at AMYLN05278022.

i. The Eurich Study

The Eurich study looked at a national medical claims database.[187] It offers little information on the relationship between Januvia and pancreatic cancer because of several limitations. First, pancreatic cancer was not an endpoint of the study, so it is impossible to tell exactly what effect, if any, Januvia had on the risk. *Id*. Second, the study was short term and the study itself concludes that long term safety of Januvia *cannot be assessed* from the study. *Id*. Third, the populations studied were of middle aged patients; elderly populations are the most at risk for pancreatic cancer. *Id.*

ii. The Gokhale Study

The Gokhale study was specifically designed to address the question of Januvia and pancreatic cancer.[188] [redacted][190] While the paper failed to find an increased risk of pancreatic cancer, the study acknowledges that its results only apply to short term use of Januvia, and the study only used one database, Medicare.[191]Since most individuals use diabetes medications on a long term basis, the study does not meaningfully address the risk of pancreatic cancer in the relevant population. In this case, the short drug exposure time could not be expected to produce any events. [redacted].[192]

[187] Eurich, DT., et al., Comparative Safety and Effectiveness of Sitagliptin in Patients with Type 2 Diabetes: Retrospective Population Based Cohort Study. BMJ. 2013 Apr 25; 346: 1-10.
[188] Gokhale, M., et al. Dipeptidyl-Peptidase-4 Inhibitors and Pancreatic Cancer: A Cohort Study. Diabetes.Obes.Metab. 2014 Dec; 16(12): 1247-1256.
[189] Proposal for UNC-CH to Serve as the Coordinating Center for an Analysis of the Relationship between the Use of Incretin-based Therapies and Cancer Incidence. MRKJAN10000690778.
[190] MRKJAN0000576096.
[191] Gokhale, M., et al. Dipeptidyl-Peptidase-4 Inhibitors and Pancreatic Cancer: A Cohort Study. Diabetes.Obes.Metab. 2014 Dec; 16(12): 1247-1256.
[192] Yu Deposition p. 231:10 – 231:19.

iii. The Monami Study

The Monami paper was actually a meta-analysis of clinical trial results. A meta-analysis of controlled clinical trials can be considered a form of ES. [193] This paper also speaks to short term effects and fails to provide useful information on long term effects. As stated in the paper's conclusion:

> The present meta analysis seems to exclude any relevant short term effect of DPP4i on the incidence of cancer and suggest a possible protection from cardiovascular events. This result should be interpreted with caution as those events were not the principal endpoint, the trial duration was short, and the characteristics of patients included could be different from routine clinical practice.

Again, this study is of limited value. It neither establishes a lack of association between Januvia and pancreatic cancer in long-term use, nor rules out an increased risk.

iv. The Odyssee Study

The Odyssee study was an observational non-randomized open label study conducted in France.[194] [redacted] *Id.* at 424. Again, this study, alone, does not support a conclusion, [redacted] something that the FDA would consider to be relevant when examining a CBE regarding pancreatic cancer.

c. Novo Nordisk's Epidemiological Studies

I reviewed two studies of interest for Victoza: [redacted] My opinion is that both studies are uninformative for reasons similar to those stated for the Byetta studies. Contrary to the assertions of Novo Nordisk, these studies also do not rule out an increased risk of pancreatic cancer resulting from Victoza use.

---

[193] Monami, M., et al., Safety of Dipeptidyl Peptidase-4 Inhibitors: A Meta-Analysis of Randomized Clinical Trials. Curr.Med.Res.Opin. 2011 Nov; 27(3): 57-64.

[194] Observational Study of the Treatment and Follow-up of Patients with Type Il Diabetes Receiving Treatment with Sitagliptin or Metformin/Sulfonylurea Dual Therapy. MRKJAN0001072125.

[195] [redacted] NOVO-00118902.

i. Victoza Optum Study

The Victoza Optum study uses health insurance database claims information to determine the incidence rate of diseases.[196] The primary outcome of interest in the study was assessment of the risk of medullary thyroid cancer in patients taking Victoza. Pancreatic cancer was included as a secondary outcome of interest. *Id.* at 25. The Optum study suffers from two main weaknesses: it is not sufficiently powered to detect differences in the incidence of pancreatic cancer; and it used an "intent-to-treat" analysis that severely limits the sensitivity of this study.

In the published version of the paper, the authors acknowledge that "the median follow-up time for the study subjects was 15 months. While the length of this period may be sufficient for acute pancreatitis, it may be inadequate for pancreatic cancer." [197] Furthermore, Alan Moses, the Global Chief Medical Officer for Novo Nordisk, admitted at his deposition that the Optum study was neither designed nor powered to determine the causal relationship between Victoza and pancreatic cancer. Rather, Optum was designed to assess Thyroid Cancer.[198]

Optum also used an "intent-to-treat" analysis, which is a "design in which initiators of a study drug [are] assumed to be on that drug until they [experience] a study outcome…."[199] [redacted]

[redacted]

[196] Liraglutide Safety and Surveillance Program using AperioLive and the Optum Research Database. NOVO-01022167.
[197] Funch, D., et al., A Prospective, Claims-based Assessment of the Risk of Pancreatitis and Pancreatic Cancer with Liraglutide Compared to Other Antidiabetic Drugs. Diabetes.Obes.Metab 2014 Mar; 16(3): 273-275.
[198] Moses Deposition p. 103:21 – 104:11.
[199] Funch, D., et al. A Prospective, Claims-based Assessment of the Risk of Pancreatitis and Pancreatic Cancer with Liraglutide Compared to Other Antidiabetic Drugs. Diabetes.Obes.Metab 2014 Mar; 16(3): 273-275.

[redacted]

The two main weaknesses discussed above, coupled with the authors' additional concern that "the accuracy of claims-based pancreatic cancer diagnosis is unclear,"[201] makes any reliance upon the Victoza Optum study highly problematic.

ii. Victoza CPRD Study

[redacted][203] Only 1,171 patients received Victoza during the most recent result set (*Id.*), making the study significantly underpowered to detect any meaningful difference in pancreatic cancer incidence rates.

5. Epidemiology: Meta-Analyses

a. European Medicines Agency, Assessment report for GLP-1 based therapies

On July 25, 2013, the European Medicines Agency ("EMA") examined some of the available literature and published an *Assessment report for GLP-1 based therapies.*[204] The report was intended to examine Butler, et al., Marked Expansion of Exocrine and Endocrine Pancreas

[200] [redacted] NOVO- 01022167.

[201] Funch, D., et al., A Prospective, Claims-based Assessment of the Risk of Pancreatitis and Pancreatic Cancer with Liraglutide Compared to Other Antidiabetic Drugs. Diabetes.Obes.Metab. 2014 Mar; 16(3): 273-275.

[202] [redacted] NOVO-02153958.

[203] [redacted] NOVO-00118902.

[204] European Medicines Agency, Assessment Report for GLP-1 Based Therapies: Review Under Article 5(3) of Regulation (EC) No 726/2004. (July 25, 2013), available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/08/WC500147026.pdf.

with Incretin Therapy in Humans with Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon-Producing Neuroendocrine Tumors, Diabetes. 2013;62:2595-2604, discussed above. Butler et al had reported an increased risk of pancreatitis and cellular changes in patients treated for type 2 diabetes with GLP-1 based on histological examinations of 34 pancreata obtained from brain dead organ donors. The pancreata of the eight individuals with Type 2 diabetes who were treated with sitagliptin (n = 7) or exenatide (n = 1) for a year or more were compared to 12 pancreata from T2DM patients treated with other therapies and 14 pancreata from non-diabetic individuals. In their publication, the investigators describe a number of tissue findings in the diabetic patients treated with GLP-1 based therapies compared to control group. Butler et al concluded that their data suggested an increased risk of pancreatitis and neoplasms associated with incretin treatment. [205] This report did not contain a meta-analysis, though his group later published an article that included a meta-analysis (Diabetes Care 2013). The EMA report included its own meta-analysis.

The article discussed of Dr. Butler's findings, as well as non-clinical and clinical data, in the possession of the EMA, and an "*ad hoc* expert meeting." In conclusion, the EMA stated the following:

> [T]he results of the study by Butler et al are not considered to constitute a new safety signal for the GLP 1 based therapies with respect to pancreatic safety. This is further supported by the review of available preclinical and clinical data.
>
> However, due to the mechanism of action, there are still some uncertainties with respect to long term pancreatic safety associated with these products and updates to the risk management plans (including planned and ongoing studies) and harmonisation of warnings in the product information should be taken forward. [206]

Of importance, the article also stated that "[I]t is noted that marketing authorization holders are closely monitoring for effects on the pancreas." This statement reflects that like the FDA, the EMA also relies on the drug's manufacturer to gather accurate information concerning the risk of pancreatic cancer and to adequately communicate that information to regulatory authorities, doctors and patients. The EMA also clearly considers its investigation to be ongoing.

---

[205] Butler, AE., et al., Marked Expansion of Exocrine and Endocrine Pancreas with Incretin Therapy in Human with Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon Producing Neuroendocrine Tumors. Diabetes. 2013 Jul; 62(7): 2595-2604.

[206] European Medicines Agency, Assessment Report for GLP-1 Based Therapies: Review Under Article 5(3) of Regulation (EC) No 726/2004. (July 25, 2013), available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/08/WC500147026.pdf.

The EMA article is information the FDA would consider relevant when evaluating a CBE for pancreatic cancer. Of interest, the article notes that the mechanism of action still causes uncertainty with respect to long term pancreatic safety, or in other words, that the mechanism of action is biologically plausible.

Also of interest, despite one of the article's conclusions that the study by Butler, et al is not considered to constitute a new safety signal, the article also states that "[f]urthermore, pancreatic cancer must be included as a potential risk for all products for which it is not already reflected in the risk management plans." [redacted][207]

According to the EMA's *Questions and Answers on the Risk Management Plan (RMP) Summary*, Risk Management Summaries are in the process of being published.[208] If pancreatic cancer is included in the Summary, distribution will put this information into the hands of physicians and patients. The timing of this request (after publication of the EMA article), along with the article itself, suggests that the EMA still consider pancreatic cancer to be a potential risk and has not concluded its investigation.

It is worth pointing out that the article does not reflect a complete analysis of all of the relevant information. For example, an examination of the article reveals that the EMA likely did not yet have some of the non-clinical and clinical data that the FDA was also missing, as discussed above. Given the timing of the EMA's report (July 2013), the EMA also did not have the benefit of Health Canada's assessment, as discussed below. In addition, EMA did not have the benefit of Dr. Madigan's report, referenced above. EMA also did not have the benefit of some of the recently published medical literature, also discussed in this report. In turn, although a relevant piece of information, it is my opinion that the FDA would not have taken any comfort in the EMA article, and would not have relied on it to deny a CBE regarding pancreatic cancer.

[207] MRKJAN0001369356, NOVO-00949394, and AMYLN05318927.
[208] European Medicines Agency, Questions and Answers on the Risk Management Plan (RMP) Summary. (May 5 2014), available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/05/WC500166101.pdf.

b. Health Canada

[redacted]

[209] Marketed Health Products Directorate Health Products and Food Branch Health Canada, Signal Assessment:DPP4 inhibitors (gliptins) Pancreatic carcinoma. (November 12, 2013), MRKJAN 10000306295.

[redacted]

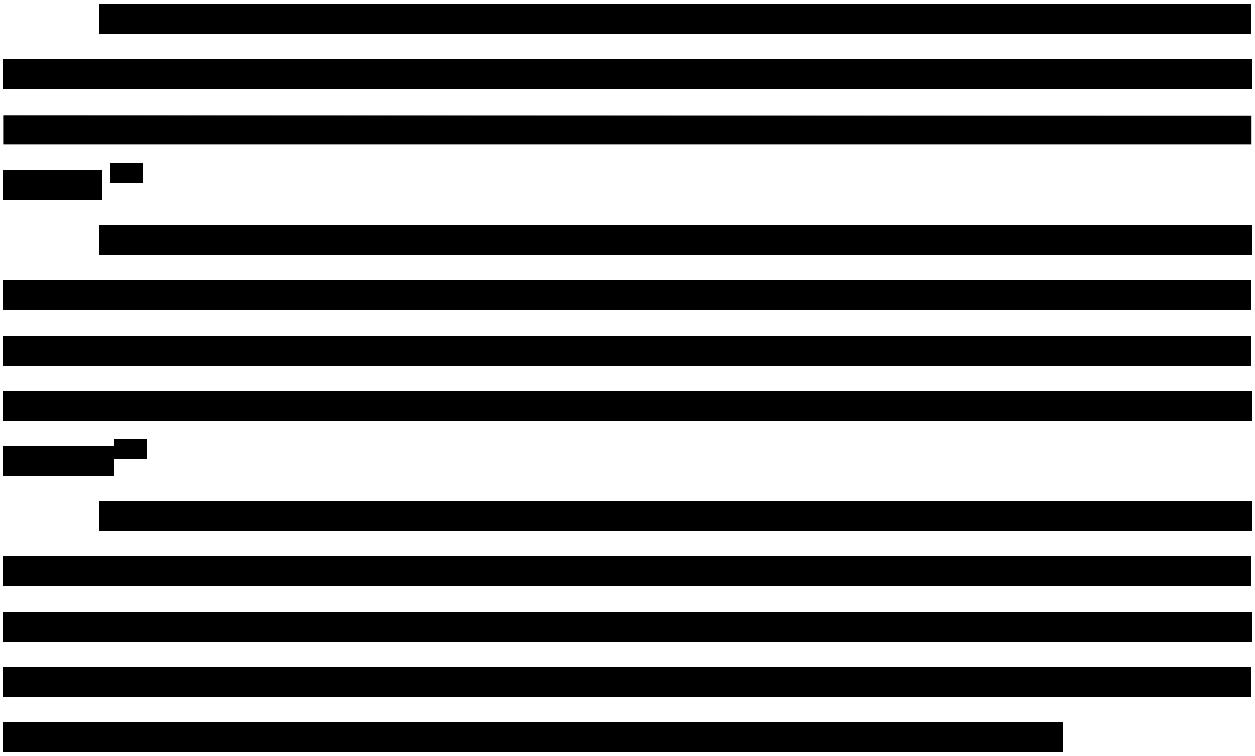
[210] Health Canada Advisement Letter for Januvia. (November 6, 2013), MRKJAN10000310621.
[211] Marketed Health Products Directorate Health Products and Food Branch Health Canada, Signal Assessment: DPP4 inhibitors (gliptins) Pancreatic carcinoma. (October 8, 2014), MRKJAN0003072498.

[redacted]

Id. Byetta and Onglyza currently warn of pancreatic cancer in their CPM. Specifically, the Byetta Product Monograph warns in the Post-Market Adverse Drug Reactions section which, as with the FDA, does not require proof of a causal relationship. The label notes:

> **Neoplasms benign, malignant and unspecified (incl cysts and polyps):** Adenocarcinoma pancreas, Benign neoplasm of thyroid gland, Benign pancreatic neoplasm, Pancreatic carcinoma, Pancreatic carcinoma metastatic, Pancreatic carcinoma non-resectable, Pancreatic carcinoma recurrent, Pancreatic carcinoma

stage II, Pancreatic neoplasm, Pancreatic neuroendocrine tumour, Pancreatic neuroendocrine tumour metastatic, Thyroid adenoma, Thyroid cancer, Thyroid cancer metastatic, Thyroid neoplasm.[213]



The Health Canada Signal Assessment is particularly important here for two reasons. First, the FDA generally recognizes Health Canada as performing high quality regulatory work that merits close scrutiny and serious consideration by FDA. Second, it is specifically recognized that Health Canada has taken an active role in evaluating the safety of the incretin mimetic drugs.

A good example of the regard FDA has for Health Canada's analysis with respect to the incretin mimetics is found in the letters in which FDA denied appeals by Amylin regarding the approval of Bydureon (exenatide extended release). Amylin was appealing FDA's decision to require additional studies of Bydureon before approval. Amylin's second appeal on this issue was denied in a May 11, 2011 letter from John Jenkins, Director of the FDA's Office of New

[213] Byetta Canadian Product Monograph available online at: http://www.bmscanada.ca/static/products/en/pm_pdf/Byetta_PM_E_%202013-07-3_APP_CLN.pdf.
[214] Marketed Health Products Directorate Health Products and Food Branch Health Canada, Signal Assessment: DPP4 inhibitors (gliptins) Pancreatic carcinoma. (October 8, 2014), MRKJAN0003072498.
[215] Health Canada Advisement Letter for Januvia. (October 1, 2014), MRKJAN0003072602.

Drugs, to Amylin's Chief Medical Officer, Dr. Orville Kolterman.[216] The letter makes it clear that Amylin failed to disclose to the FDA a study "requested by Health Canada as important safety data in support of the planned marketing application for Byetta in Canada[.]" *Id*. at p. 2. FDA noted that it "first became aware of [the Health Canada study] when Health Canada contacted FDA to discuss safety concerns based on their review of the study results[.]" *Id*. FDA expressed frustration that Amylin had failed to disclose this important safety information:

> I can think of no good explanation for your failure to inform [FDA] of the data from [the Health Canada study] in a timely manner so those data could be reviewed as part of the ongoing evaluation of the safety of Byetta and in the assessment of the safety of Bydureon…. [Amylin's conduct is] not consistent with FDA's requirement that all pertinent safety data be submitted for our review in support of marketing applications.

Id. at p. 3. Amylin's appeal was then denied.

Based on my experience at the FDA and the emphasis that FDA has placed on the work being done by Health Canada on the incretin mimetics, it is my opinion that the Health Canada Signal Assessment would be extremely significant and compelling to FDA – both from a scientific and a competitive standpoint. [redacted] Whether all this information was in the possession of the FDA or not at the time of the NEJM article is, however, not the point here. It should have been clear to the manufacturers by the time the NEJM article came out that they needed to take action on their labels to protect patients who were using their drugs. The manufacturers cannot fulfill their obligations under the FDA's regulatory system by keeping their heads in the sand and waiting for the FDA to act, [redacted] The manufacturers also cannot point to the NEJM article to say that their hands were tied. The signal assessment, along with all of the other information cited above, provides more than ample support for my conclusion that FDA would not reject a manufacturer's CBE adding pancreatic cancer risk information to the label of its incretin medication.

[216] Ltr. from U.S. Food and Drug Association to Amylin. (May 11, 2011), LILLY01786889.

C. PANCREATIC CANCER IS AN EXTREMELY SERIOUS ADVERSE EVENT

I have discussed two of the key considerations for determining the appropriateness of a CBE—biologic plausibility and strength of signal. The third consideration, the seriousness of the condition, is perhaps the most important consideration. A highly plausible and clearly drug associated adverse event that is not serious obviously does not require the kind of handling that a serious adverse condition requires. There are drugs that may cause hiccups, but a manufacturer would typically not be obligated to expedite the insertion of this information in its label. On the other hand, this case involves one of the most feared of all medical conditions.

Pancreatic cancer is one of the most deadly cancers. It usually starts in the ducts that carry the pancreatic juices to the stomach. This is called *exocrine* pancreatic cancer, and is the type of cancer involved in this case. Although much less common, pancreatic cancer can also start in the pancreatic islet cells that produce hormones that circulate throughout the body. This second type of pancreatic cancer is called *endocrine* pancreatic cancer, or islet cell cancer. Cancers of the endocrine tissue are much rarer, but are often easily detected and treated because they secrete tell-tale hormones. Our discussion here is about the more common form of exocrine pancreatic cancer involved in this case.

As noted previously, the incidence of pancreatic cancer is approximately 12.3 per 100,000 in the general population.[217] There were an estimated 46,420 new cases of pancreatic cancer in 2014, with an estimated 39,500 deaths. *Id*. The disease has a five-year survival rate of only 6.7%. *Id*. The exocrine pancreatic cancer involved in this case is particularly deadly because medical science has not yet found a way to reliably detect it at a stage at which it can still be treated successfully. Pancreatic cancer is also often regarded as a very painful disease that leads to a painful death.

It is my opinion that given our inability to reliably detect pancreatic cancer at a treatable stage, the high mortality rate of pancreatic cancer, and the evidence detailed above linking the incretin medications to the development of pancreatic cancer, the FDA would not reject a CBE

[217] SEER Stat Fact Sheets: Pancreas Cancer, available online at: http://seer.cancer.gov/statfacts/html/pancreas.html.

adding risk information for pancreatic cancer. This is precisely the type of risk information that prescribing physicians and patients want in order to make informed decisions.[218]

XI. A PROPERLY SUPPORTED CBE, IMPLEMENTING A LABEL CHANGE FOR PANCREATIC CANCER, WOULD NOT BE REJECTED BY THE FDA

When the FDA reviews a labeling change relating to warnings or adverse reactions, the FDA's focus is on whether the proposed information could "have implications for prescribing decisions or for patient management" or might "be useful to health care practitioners making treatment decisions and monitoring and advising patient."[219] [220] As noted above, because the manufacturer bears primary responsibility for ensuring the adequacy of its drug's labeling, when a manufacturer proposes adding a new warning or new risk information, the FDA's typical practice is to defer to the manufacturer's analysis suggesting that scientific evidence exists supporting the change.

The FDA has no established policy for *prohibiting* warnings and risk information; rather, all of the existing policies exist to *encourage* and *enable* manufacturers to add warnings and risk information as soon as such are warranted. In 2007, the Food and Drug Administration Amendments Act authorized the FDA to order certain drug application holders to make safety-related labeling changes. The purpose of this Act was to give the FDA more power "to require safety labeling changes," i.e., to compel *more* safety information, not less, because previously the FDA would have been limited to various cumbersome methods of negotiating a label change. The FDA's new power, however, does nothing to alter the manufacturers' responsibility for their labels, and does not alter the FDA's long-standing practice encouraging and enabling manufacturers to warn about safety risks, even in the face of conflicting data.

Indeed, it is unclear how the FDA could prohibit a manufacturer from adding a warning or risk information, as the FDA has no guidance or practices relating to "misbranding" prosecutions for *excessive* warnings, and I have never heard of such a prosecution occurring.

---

[218] This is well understood by the incretin manufacturers. Dr. John Buse, a consultant to the manufacturers involved in this case, put it this way: **"Pancreatic cancer is freakishly scary to patients and providers."** (MRKJAN10000312005).

[219] Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format (October 2011), p. 3.

[220] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006), p. 2.

A. THE FDA HAS NEVER SHOWN ANY OPPOSITION TO PANCREATIC CANCER WARNINGS OR RISK INFORMATION, MUCH LESS SHOWN AN INTENT TO PROHIBIT THE SAME

Based on the information I reviewed, the manufacturers of Byetta, Januvia, Janumet, and Victoza have never proposed adding pancreatic cancer as an adverse reaction. Correspondingly, the FDA has never reviewed, much less rejected, a proposed label change listing pancreatic cancer as an adverse reaction. The FDA has similarly never informed the manufacturers that their drugs would be misbranded if they carried information about pancreatic cancer.

As I mentioned above, the FDA's normal practice is to permit manufacturers to add adverse reactions and warnings as they see fit. When the FDA objects to an adverse reaction or warning, it typically does so because it would like to alter the wording, or perhaps elevate a proposed adverse reaction to a warning[221], rather than to prohibit the manufacturer from mentioning an adverse reaction or warning about the risk of an adverse reaction.

As stated by the Safety Labeling Change Guidance, explaining the process prior to 2007[222] for *when the FDA was demanding a warning*:

> FDA typically learned of the potential for such serious risks from a variety of sources, including FDA's adverse events reporting systems (see list of sources in Appendix A). In most cases, application holders responded to these requests for labeling changes by negotiating appropriate language with FDA staff to address the concerns and then submitting a supplement or amended supplement to obtain approval of the changes. Negotiations were often protracted, and FDA had few tools at its disposal to end negotiations and require the changes.[223]

Similarly, when a manufacturer proposes an adverse reaction or warning, the ensuing process involves a negotiation over the appropriate language, rather than a prohibition on the risk information.

Lacking any actual submission of a label change, much less an actual response from the FDA showing any *intent to prohibit* a label change, I do not believe there is any sound basis on which to conclude the FDA would prohibit a pancreatic cancer warning or adverse reaction

---

[221] [redacted]. See U.S. Food and Drug Administration Ltr. to Merck. (October 16, 2009), MRKJAN0000210624.

[222] The change in 2007 related to the FDA's power to compel a warning (rather than, for example, initiating a misbranding prosecution, which is rare, and which to the best of my knowledge has never occurred on the basis of the manufacturer *adding* a warning).

[223] Guidance for Industry Safety Labeling Changes-Implementation of Section 505(o)(4) of the FD&C Act (July 30, 2013).

supplement, if proposed by the drug's manufacturer. Such is pure speculation, and is contrary to the FDA's typical practices and the guidance materials upon which its reviews rely.

1. The FDA Would Not Have Prohibited the Manufacturers from Adding Pancreatic Cancer to the Adverse Reactions Section

In general, the purpose of the Adverse Reaction section is not to settle scientific debates, nor to await indisputable evidence of a causal link, but rather to inform prescribers of any adverse reactions spontaneously reported for which "there is some basis to believe there is a causal relationship." 21 CFR § 201.57(c)(7). The guidance reiterates that "some basis" is "a matter of judgment," including factors such as "(1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) the extent of dose-response, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the timing of the event relative to the time of drug exposure, (6) existence of challenge and dechallenge experience, and (7) whether the adverse event is known to be caused by related drugs."[224]

As described throughout this report, the Incretin mimetics easily meet factors (1), (2), (4), and (5) for pancreatic cancer, because they have well above the expected adverse event rate, a plausible biological mechanism, and a temporal association in the reported cases. Factor (3) requires more thorough data collection than appear to be available[225], however, the Japanese and renally-impaired cases discussed above are starting to provide some dose response data; (6) cannot be done in the case of pancreatic cancer risk, and (7) is a question of how one defines "known to be caused." In my opinion, the incretin mimetics can be "known to cause" pancreatic cancer given the available evidence.

It is also my opinion that the FDA, in reviewing a labeling submission, would find that risk information about pancreatic cancer would "be useful to health care practitioners making treatment decisions and monitoring and advising patient." [226]

For example, with regard to prescribing decisions, a physician might consider this risk information if they were treating a patient who is a smoker, drinks alcohol excessively, who is

[224] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006).
[225] That said, the FDA 2 study, which was submitted and published after the NEJM article, did in fact show a dose-dependent pancreatic injury in animal models.
[226] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006), p. 2.

overweight, or who was exposed to chemicals used in metal refining, all of which are known to be risk factors for pancreatic cancer. Or, the patient, given this information, may be more likely motivated to alter their behavior while on the medication and thus lower their risk. Additionally, age, gender (men more than women), race, family history, certain genetic markers, chronic pancreatitis, cirrhosis of the liver, and infection with *H. pylori* are all believed to increase the risk of pancreatic cancer, and so a physician treating such a patient, or patient of that nature, might consider that information in choosing which medication to use.[227] In addition, it should be kept in mind that there are a number of other options available to prescribing physicians and patients to treat Type 2 diabetes besides incretin mimetics.

Further, if a physician was aware that pancreatic cancer was a potential risk of a medication, they could alter their management of the patient to more vigilantly look for evidence of cancer masses or fluid buildup in the abdomen, jaundice, prominent lymph nodes, or perform a variety of tests, such as blood biomarkers, and scans, including CT, MRI, ultrasound, and others.[228]

The Adverse Reaction section is broken into two components, 6.1 for "Clinical Trial Experience" and 6.2 for "Post-Marketing Experience." I analyzed each specifically below.

a. "Clinical Trial Experience"

The Clinical Trial Experience begins with a disclaimer, per the Guidance, "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."[229] This disclaimer is there because the purpose of the Adverse Reaction section is not to settle scientific debates, nor to await indisputable evidence of a causal link, but rather to inform prescribers of any adverse reactions identified in clinical trials that are *plausible* or which *occurred at a frequency above that expected*. *Id.*

---

[227] American Cancer Society, What are the Risk Factors for Pancreatic Cancer. available online at: http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-risk-factors.
[228] American Cancer Society, How is Pancreatic Cancer Diagnosed. available online at: http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-diagnosis.
[229] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006).

Further, the Guidance says, with regard to adverse reactions arising from clinical trials, "Serious, low-frequency adverse events generally will be listed when there is reason to suspect that the drug may have caused the event," with typical reasons including "(2) plausibility in light of the drug's known pharmacology, (3) occurrence at a frequency above that expected in the treated population…" *Id.* at 5.

i. "Clinical Trial Experience" – The Victoza Example

We can see an example of this process at work on the Victoza prescribing information, in the context of papillary thyroid carcinoma and malignant neoplasms. The Victoza prescribing information includes:

> *Papillary thyroid carcinoma*
> In clinical trials of Victoza®, there were 7 reported cases of papillary thyroid carcinoma in patients treated with Victoza® and 1 case in a comparator-treated patient (1.5 vs. 0.5 cases per 1000 patient years). Most of these papillary thyroid carcinomas were <1 cm in greatest diameter and were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings on protocol-specified screening with serum calcitonin or thyroid ultrasound.

Then, later in 6.1, the information includes:

> In a pooled analysis of clinical trials, the incidence rate (per 1,000 patient-years) for malignant neoplasms (based on investigator-reported events, medical history, pathology reports, and surgical reports from both blinded and open-label study periods) was 10.9 for Victoza®, 6.3 for placebo, and 7.2 for active comparator. After excluding papillary thyroid carcinoma events [see Adverse Reactions (6.1)], no particular cancer cell type predominated. Seven malignant neoplasm events were reported beyond 1 year of exposure to study medication, six events among Victoza®-treated patients (4 colon, 1 prostate and 1 nasopharyngeal), no events with placebo and one event with active comparator (colon). Causality has not been established.[230]

Consistent with the focus on providing information useful to physicians and patients, the label makes no effort to engage in a sophisticated epidemiological analysis of whether the papillary thyroid carcinoma events or the malignant neoplasm events detected in the trial are statistically significant or whether they establish a causal link. Indeed, the label expressly says "causality has not been established." *Id.* There is no need to establish causality to include risk information in 6.1: the question is whether there is reason to suspect that the drug may have caused the event (e.g., by examining plausibility and the frequency with which it occurs). As

[230] Victoza Label available online at:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf.

explained throughout this report, it is abundantly clear that we have ample "reason to suspect" that the incretins may cause pancreatic cancer.

ii. "Clinical Trial Experience" – The Manufacturers Could Add Pancreatic Cancer Risk Information

As explained above in this report, each of the manufacturers has ample clinical trial data to include information about pancreatic cancer events in its clinical trials. [redacted]"[231] Even putting aside Novo's inappropriate analysis of their clinical trial data (which would allow for years of unaccounted incretin mimetic exposure), [redacted], that 4:1 imbalance alone is sufficient to support inclusion in section 6.1. Once biological plausibility is added to the analysis, the case for inclusion in 6.1 becomes even stronger.

[redacted] The same is true for Novo's imbalance of 5:1 in liraglutide exposed patients. Amylin's imbalance of 6:2, or their combined 17:6 imbalance. Again, those imbalances are sufficient to show "occurrence at a frequency above that expected in the treated population." Combined with "plausibility in light of the drug's known pharmacology," there is ample support for inclusion in section 6.1.

The NEJM article addressed some of this clinical data and its relationship to pancreatic cancer in the following sentences[232]:

> Clinical safety databases reviewed by the FDA included data from more than 200 trials, involving approximately 41,000 participants, more than 28,000 of whom were exposed to an incretin-based drug; 15,000 were exposed to drug for 24 weeks or more, and 8500 were exposed for 52 weeks or more. … A pooled analysis of data from 14,611 patients with type 2 diabetes from 25 clinical trials in the sitagliptin database provided no compelling evidence of an increased risk of pancreatitis or pancreatic cancer. … The reported incidence of pancreatic cancer was 5 and 12 cases, respectively, in the drug and placebo groups in the SAVOR trial, with no incidence of pancreatic cancer in either group in the EXAMINE

[231] [redacted] NOVO-00948679.

[232] Egan, A., et al., Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment. N.Eng.J.Med. 2014 Feb. 27; 370(9): 794-797.

> trial. … The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. … Ongoing strategies include systematic capture of data on pancreatitis and pancreatic cancer from cardiovascular outcome trials and ongoing clinical trials, which should facilitate meta-analyses, and accumulation of further knowledge regarding these signals in the future.

Initially, the materials in this case suggest that those "clinical safety databases" may include erroneous information about the exposure time of patients, as well as inadequate follow-up, and that [redacted] Were the manufacturers to submit a CBE, they would need to provide information that was both complete and accurate in support of the change.

But those issues are not critical to the larger issue: nothing in the above suggests the FDA would prohibit any of the manufacturers from adding risk information about pancreatic cancer to section 6.1 of their respective labels. The purpose of 6.1 is to identify, for the benefit of prescribers and patients, adverse events recognized in the trials that are *plausible* or which *occurred at a frequency above that expected*, and the NEJM article itself notes an imbalance found by the SAVOR trial, which alone is sufficient. The NEJM article further notes that it is monitoring pancreatic cancer data from ongoing clinical trials, which is further evidence that the FDA believes a link is possible and would not oppose a labeling change made by the manufacturers.

The FDA's recitation that the Engel analysis merely "provided no compelling evidence of an increased risk" is a far higher bar than the standard for inclusion in 6.1, which is "occurrence at a frequency above that expected in the treated population." Stated another way, the FDA's recognition that the Engel data does not prove a causal relationship in no way suggests the FDA would reject risk information derived from clinical trials — it shows only that the FDA is not mandating a labeling change at this time. As is the FDA's practice, and as confirmed by its most recent Draft Guidance on the FDAAA,[233] the FDA's power to *compel* a labeling change is entirely separate from their review of voluntarily labeling changes proposed by manufacturers.

[233] Guidance for Industry Safety Labeling Changes-Implementation of Section 505(o)(4) of the FD&C Act (July 30, 2013). "This guidance does not address labeling supplements submitted voluntarily by an application holder. Application holders may submit labeling supplements for review at any time and without prior notification to FDA." p. 2.

c. "Post-Marketing Experience"

The Post-Marketing Experience begins with a disclaimer, per the Guidance, "Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure."[234] This disclaimer is there because the purpose of the Adverse Reaction section is not to settle scientific debates, nor to await indisputable evidence of a causal link, but rather to inform prescribers of any adverse reactions spontaneously reported for which "there is some basis to believe there is a causal relationship," which I described above. Specific to spontaneous reports, the Guidance notes:

> Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug. When an adverse reaction identified from spontaneous reporting is included in the labeling, the number of spontaneous reports ordinarily is not cited, because the number can quickly become outdated. If the number of reports is cited, the period of observation should be stated.

Id. at 8. Importantly, however, the Guidance discourages manufacturers from determining which Post-Marketing adverse events to warn about by way of subjective interpretations:

> The rate of an identified adverse reaction is ordinarily derived from all reported adverse events of that type in the database used. Determining a rate based on a subset of reported events that individual investigators believe to be causally related to drug exposure is discouraged. Excluding events from the rate calculation based on the judgment of individual investigators introduces bias and inconsistency in rate determinations.

Id. at 8-9. Stated another way, Post-Marketing Experience is intended to be derived from the raw events noticed in the field, and is not to be colored by extensive analysis of whether a causal link may exist. If an adverse reaction is reported, and there is "some basis to believe there is a causal relationship," then the adverse reaction can and should be disclosed.

[redacted]

[234] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006).

[redacted]

Returning to the factors identified by the guidance, the "seriousness of the event" for "eructation" and "flatulence" is obvious very low, [redacted] — yet, to this day, the Byetta label continues to identify, in section 6.2, "injection-site reactions," "abdominal distension, abdominal pain, eructation, constipation, [and] flatulence."

[redacted]

[235] [redacted].

[redacted] Returning to the factors identified by the guidance, the "seriousness of the event" for INR increases and bleeding is significant and potentially serious, [redacted] — yet, to this day, the Byetta label continues to identify, in section 6.2, "International normalized ratio (INR) increased with concomitant warfarin use sometimes associated with bleeding." It also identifies it in 7.2, with similar information denying a causal link, as was provided with the CBE.[237]

ii. "Post-Marketing Experience"" – The Manufacturers Could Add Pancreatic Cancer Risk Information

As explained in above in this report, each of the manufacturers has more than sufficient spontaneous adverse reaction reporting of pancreatic cancer to support an addition to section 6.2. Pancreatic cancer is as serious a condition as can be imagined, the number of reports is well

[236] [redacted]

[237] Byetta Label available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021773s036lbl.pdf. "There are postmarketing reports of increased INR sometimes associated with bleeding, with concomitant use of warfarin and BYETTA [see Adverse Reactions (6.2)]. In a drug interaction study, BYETTA did not have a significant effect on INR [see Clinical Pharmacology (12.3)]. In patients taking warfarin, prothrombin time should be monitored more frequently after initiation or alteration of BYETTA therapy. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on warfarin."

above any reasonable threshold and is trending upwards, and the strength of a causal relationship is well-established in the literature and is recognized by the FDA, which is why the FDA has recognized a "signal" and why the FDA continues to monitor that signal closely.

In 2011, before media exposure discussing pancreatic cancer, researchers in a peer-reviewed journal article had identified, through the FAERS data, that "[t]he reported event rate for pancreatic cancer was 2.9- fold greater in patients treated with exenatide compared to other therapies" and "[t]he reported event rate for pancreatic cancer was 2.7-fold greater with sitagliptin than other therapies."[238] The Institute for Safe Medication Practices subsequently performed "a disproportionality analysis of domestic, serious adverse event reports for five GLP-1 agents from July 1, 2011, through June 30, 2012," which is again prior to media exposure, and found "[t]he adjusted odds ratio for the GLP-1 group compared to the diabetes drug controls was OR 25.6 (95% CI 15.9-47.8)," which data they concluded "provide a signal for pancreatic cancer substantial enough to warrant further investigation."[239]

I am neither an epidemiologist nor a biostatistician, but these are the type of analyses upon which I, as well as reviewers at the FDA, rely. I have not seen any indication that either of these reports is so methodologically unsound that they cannot be relied upon *at all*.[240] Thus,

---

[238] Elashoff, M., et al., Pancreatitis, Pancreatic, and Thyroid Cancer with Glucagon-like Peptide-1-based Therapies. Gastroenterology. 2011 Jul; 141(1): 150-156.

[239] Institute for Safe Medicine Practices, Perspectives on GLP-1 Agents for Diabetes. QuarterWatch, April 18, 2013. Available online at: http://www.ismp.org/quarterwatch/pdfs/2012Q3.pdf.

[240] In November 2010, the United States submitted to the Supreme Court an amicus brief reiterating many important principles of adverse event reporting analysis. Brief for the United States as Amicus Curiae *Matrixx Initiatives, Inc. et al. v. Siracusona, et al.* 536 U.S. ___ (2011). As the United States reiterated, "data showing a statistically significant association are not essential to establish a link between use of a drug and an adverse effect," p. 12, and "While statistical significance provides some indication about the validity of a correlation between a product and a harm, a determination that certain data are not statistically significant—let alone, as here, the absence of any determination one way or the other—does not refute an inference of causation," p. 14. Rather, "FDA relies on a number of those factors in deciding whether to take regulatory action based on reports of an adverse drug effect," p. 16, and "FDA does not apply any single metric for determining when additional inquiry or action is necessary, and it certainly does not insist upon 'statistical significance,'" p. 19. Thus, when evaluating adverse event reports, the question is not whether the adverse event reports demonstrate an iron-clad statistical case, but whether disclosing the adverse event might "be useful to health care practitioners making treatment decisions and monitoring and advising patient." Guidance for Industry

these reports are appropriate to rely upon in concluding they suggest "the frequency of reporting," "the adverse event rate for the drug exceed[ing] the placebo rate," and the "number of reports" sufficient to support an addition to the Post-Marketing Experiences section of the label.

Additionally, in this litigation, Dr. Madigan concluded that an analysis of spontaneous reports shows a clear safety signal has existed since at least as far back as 2011 and as far back as 2008 according to company documents. My analysis shows a safety signal for exenatide in the second quarter of 2010, for sitagliptin in the third quarter of 2010, and for liraglutide in the first quarter of 2011.

Again, though I am not a biostatistician, the analysis by Dr. Madigan is the type of analysis upon which I, as well as reviewers at the FDA, rely. The methodology he utilized is consistent with the methodology used at the FDA to examine matters such as "the frequency of reporting," "the adverse event rate for the drug exceed[ing] the placebo rate," and the "number of reports" sufficient to support an addition to the Post-Marketing Experiences section of the label.

The NEJM article addressed adverse event reporting and its relationship to pancreatic cancer in the following sentences[241]:

> Both agencies committed themselves to assessing the evidence pertinent to reported adverse events, as well as any factors that might confound safety analysis in the context of antidiabetic drugs. Although the disproportionate spontaneous reporting of adverse events is commonly interpreted as a safety signal, there are inherent limitations to the ability to establish causal relationships, including the evaluation of events with high background rates, long latency periods, or a possible contribution by the disease itself. …
>
> . … The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. … Ongoing strategies include systematic capture of data on pancreatitis and pancreatic cancer from cardiovascular outcome trials and ongoing clinical trials, which should facilitate meta-analyses, and accumulation of further knowledge regarding these signals in the future.

Thus, the FDA has recognized a "signal" in the form of "disproportionate spontaneous reporting of adverse events," but — as is well-recognized in the field — the signal itself is not sufficient "to establish causal relationships," and so "accumulation of further knowledge," which

---

Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006), p. 2.

[241] Egan, A., et al., Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment. N.Eng.J.Med. 2014 Feb. 27; 370(9): 794-797. I have omitted the parts discussing clinical trials but referring only to pancreatitis, not pancreatic cancer.

includes spontaneous reporting, will be combined with other information for meta-analyses. Nothing in the NEJM article suggests the FDA would prohibit the manufacturers from adding pancreatic cancer to section 6.2; indeed, the FDA itself has recognized the very foundation of Post-Marketing Experience, which is disproportionate reporting. Whether the data "establish[es] causal relationships," an issue which the FDA has left open as it gathers further information, is a far higher threshold than the threshold imposed upon the addition of an adverse reaction to a label. If that were the standard, the majority of adverse reactions would not appear on drug labels, and Byetta would certainly not reference gastrointestinal issues or interactions with warfarin.

2. The FDA Would Not Have Prohibited the Manufacturers from Adding Pancreatic Cancer to the Warnings Section

As with the Adverse Reaction section, the purpose of the Warning section is not to settle scientific debates, nor to await definitive proof of a causal relationship, but rather to inform prescribers and patients of *serious* or *otherwise clinically significant* adverse reactions that may have implications for prescribing decisions or for patient management. As described by the FDA Guidance:

> The WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or are *otherwise clinically significant* because they have implications for prescribing decisions or for patient management.[242]

In my opinion, pancreatic cancer is a profoundly "serious" or "otherwise clinically significant" safety hazard and the FDA, in reviewing a labeling submission, would consider it as such. It is also my opinion that the FDA, in reviewing a labeling submission, would determine that a safety hazard of pancreatic cancer would have "implications for prescribing decisions or for patient management." *Id.* at 3.

For example, with regard to prescribing decisions, a physician might consider this risk information if they were treating a patient who was a smoker, who was overweight, or who was exposed to chemicals used in metal refining, all of which are believed to be risk factors for pancreatic cancer. Or, the patient may be more prone to alter their behavior while on the

[242] Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format (October 2011).

medication and thus lower their risk. Additionally, age, gender (men more than women), race, family history, certain genetic markers, chronic pancreatitis, cirrhosis of the liver, and infection with *H. pylori* are all believed to increase the risk of pancreatic cancer, and so a physician treating such a patient, or patient of that nature, might consider that information in choosing which medication to use.[243]

Further, if a physician was aware that pancreatic cancer was a potential risk of a medication, they could alter their management of the patient to more vigilantly look for masses or fluid buildup in the abdomen, look for jaundice, examine lymph nodes, or perform a variety of tests, such as blood tests, and scans, including CT, MRI, ultrasound, and others.[244]

As the Guidance continues,

> To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.

I give no opinion on the "legal" meaning of "reasonable evidence of a causal association between the drug and the adverse event," which derives from the regulation.[245] The FDA guidance suggests as potential factors: "(1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) the extent of dose-response, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the timing of the

---

[243] American Cancer Society, What are the Risk Factors for Pancreatic Cancer. available online at: http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-risk-factors.

[244] American Cancer Society, How is Pancreatic Cancer Diagnosed. available online at: http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-diagnosis.

[245] I found it worrisome that the regulatory personnel for the manufacturers were unable to even identify *who* makes such a determination, much less *how* it is done. See, e.g., the deposition of Merck's director of regulatory affairs, Eader Deposition pp. 230:12-231:17 ([redacted] … I would not be able to name top three people at Merck who make those kind of decisions. It depends."); see also the deposition of Novo's regulatory liaison for Victoza, Thompson Deposition pp. 129:21-131:1 ("Now, are you the person best suited in regulatory affairs to discuss how Novo applies the reasonable evidence of a causal association standard? A. No. Q. Who is? A. I believe that's someone in global safety. … I don't know who would be responsible for Victoza in particular."

[245] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006).

event relative to the time of drug exposure, (6) existence of challenge and dechallenge experience, and (7) whether the adverse event is known to be caused by related drugs."[246]

In practice, reasonable evidence of a causal association is a matter of clinical judgment. The question is not whether a particular medical researcher, or group of researchers, would find that a causal relationship has been definitely established. The question is if the evidence is sufficient to give a medical professional reason to believe the drug has the capacity to cause a particular harm. In many cases, postmarketing reports alone are sufficient to provide such reasonable evidence of a causal association, particularly where the reports are in excess of the rate across comparable drugs and where there is an increasing trend. When postmarketing reports are found of an adverse event "consistent with the pharmacology of the drug," i.e., biological plausibility, there is reasonable evidence of a causal association.

a. Warnings – The Pancreatitis Example

Today, the Byetta, Januvia, Janumet, and Victoza labels all carry very similar warnings about pancreatitis, a warning "based on spontaneous postmarketing reports…".[247]

[redacted]

[246] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006).

[247] Byetta Label available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021773s036lbl.pdf. Byetta's pancreatitis warning begins, "Based on postmarketing data BYETTA has been associated with acute pancreatitis…" Victoza Label available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf. Victoza's pancreatitis warning states, "Based on spontaneous postmarketing reports…" Januvia Label available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021995s028lbl.pdf. Januvia's pancreatitis warning states, "There have been postmarketing reports of acute pancreatitis."

[248] Ltr. from Merck to U.S. Food and Drug Administration. (March 5, 2009), MRKJAN0000189428.

[redacted] Later that year, pancreatitis was added to the Warnings and Precaution section of the Januvia and Janumet labels. The Warning with respect to pancreatitis reads: "Pancreatitis: There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUVIA…"

As reflected by the NEJM article, the FDA and the EMA "undertook comprehensive evaluations of a safety signal arising from postmarketing reports of pancreatitis and pancreatic cancer in patients using incretin-based drugs."[251] The article concludes, "[t]he FDA and EMA have not reached a final conclusion at this time regarding such a causal relationship" and that "both agencies continue to investigate this safety signal." *Id*. at p. 796. Importantly, the authors also found that "pancreatitis will continue to be considered a risk associated with these drugs" thereby confirming that, contrary to the manufacturers' longstanding requests, the FDA will continue to mandate that pancreatitis remain listed as a warning. *Id*. ("The FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling….").

The continued warning for pancreatitis remains despite the article's claim "that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data." There are three separate points to draw from the continued warning.

[249] Submission from Merck to U.S. Food and Drug Administration. (March 5, 2009), MRKJAN0000189623.
[250] U.S. Food and Drug Administration Ltr to Merck. (October 16, 2009), MRKJAN0000210624.
[251] Egan, A., et al., Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment. N.Eng.J.Med. 2014 Feb. 27; 370(9): 794-797.

First, it is unclear to which "assertions" the FDA is referring other than those cited by name in the article. The FDA, for example, plainly agrees in principle with the elevated spontaneous adverse event reporting found by Elashoff, hence the FDA is continuing to recognize a "signal." It would not be proper to evaluate the FDA's approach to a proposed warning by speculating about the FDA's view on particular pieces of scientific literature or on particular media reports beyond those specifically referenced. Stated another way, the FDA's disagreement with unspecified "assertions" in the public domain is simply not comparable to an FDA rejection of a proposed warning.

Second, it is unclear what "current data" the FDA reviewed. The FDA describes generally what it has reviewed and cites to several specific things, but as noted elsewhere in this report, there is no way to confirm exactly what the FDA received or reviewed and it does not appear to have had available to it the full body of scientific data available to the manufacturers. [redacted] because I understand that it was not in the manufacturers' NDA files. As a further example, FDA did not appear to have the FDA 2 study showing that Byetta can cause in rodents the same type of pancreatic injury associated with pancreatic cancer in humans, because the FDA 2 study was submitted for publication months after the NEJM article. As another example, FDA did not appear to have each manufacturer's clinical trial pancreatic cancers, [redacted]

Third, and most importantly in this present context, the existence of conflicting data on causal association — and even the FDA's own apparent belief that such a causal association has not been established — does not preclude a manufacturer from warning about a risk. Indeed, in such circumstances, a manufacturer can nonetheless be ***required*** to warn about such a risk. As the FDA noted in its 2013 Guidance, "21 CFR 201.57(c)(6) requires that prescription drug labeling be 'revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug.'" "Reasonable evidence" includes *conflicting* evidence; such is the very point of the reminder, "a causal relationship need not have been definitively established" before such a warning is mandated.

b. Warnings – The Manufacturers Could Add A Pancreatic Cancer Warning

As I opined above, pancreatic cancer is plainly a serious hazard. On the basis of the spontaneous post-marketing reports alone, the manufacturers could add a warning regarding pancreatic cancer, much as the drugs currently carry for pancreatitis. When the extensive preclinical, nonclinical, and clinical data evidence is considered as well, the "reasonable evidence" for a warning is apparent.

The FDA differs in some ways from Health Canada, but the underlying science and general regulatory approaches are the same. FDA takes very seriously the findings of other creditable authorities, particularly Health Canada. The FDA's guidance on Safety Labeling Changes, for example, specifically identifies as a source of new safety information "Communications with foreign regulatory authorities regarding postmarket analysis of adverse reactions associated with drugs approved in their countries."[252] [redacted] The FDA's own nonclinical studies, such as FDA 2, provided further animal evidence consistent with the same.[253] The additional data I have outlined here further shows plausibility and disproportionate adverse event reporting. Together, this evidence is more than sufficient to show reasonable evidence of a causal association.

The NEJM article does not demonstrate that FDA would reject a pancreatic cancer warning; rather, it shows quite the opposite. As stated above, the purpose of the Warnings section is "to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or are *otherwise clinically significant* because they have implications for

[252] Guidance for Industry Safety Labeling Changes-Implementation of Section 505(o)(4) of the FD&C Act (July 30, 2013), p. 16.

[253] See FDA 2, e.g., "Consistent with [Butler et al.'s] human data, the present study generated non-clinical evidence of different types of exocrine pancreatic cells (acinar, centroacinar, ductal cells, and even interstitial cells) undergoing proliferation.

prescribing decisions or for patient management." The article shows how the FDA not only allows warnings, but sometimes mandates them (as with pancreatitis), in the face of conflicting evidence, even where the FDA has not yet seen data establishing a causal link.

By way of the 2013 Communication, and the NEJM article, the FDA itself is taking proactive measures to alert prescribers and patients that a signal for pancreatic cancer has been detected, is being evaluated, and a causal association cannot be ruled out. These two public statements are evidence of the FDA's *willingness to alert the public of a pancreatic cancer risk*, and thus also evidence that the FDA would permit a pancreatic cancer warning.

Under the FDA's policies and practices, if the manufacturers were to propose a pancreatic cancer warning, it is my opinion the FDA would not prohibit it.

XII. CONCLUSIONS

As shown above, applying the FDA's practices with regard to labeling information, there is ample evidence the promotion of pancreatic cancer is scientifically plausible and consistent with the pharmacology of incretin mimetics; the available body of nonclinical, clinical, and epidemiological evidence is sufficiently strong to constitute reasonable evidence that incretin mimetics can cause pancreatic cancer; and, the condition of pancreatic cancer is so serious that a further measure of caution is needed in warning prescribers and patients of this potential risk. At any point up to the present, the manufacturers could have submitted a CBE adding pancreatic cancer as an adverse reaction, a warning, or both, and the FDA would not have prohibited them from doing so.

The manufacturers' contention that they can evade their responsibility to provide appropriate risk information because, they speculate, the FDA would prohibit them from doing so, is unsound and contrary to the FDA's written Guidances and actual practices. Specifically, the manufacturers cannot point to the NEJM article, much less to the Citizen's Petition, to absolve themselves from taking responsibility for their own drug labels or to believe the FDA would prohibit them from acting in the best interests of the medical community, prescribing physicians, and patients using their incretin medications.

December 15, 2014

G. Alexander Fleming, M.D. Date

XIII. APPENDICES

Appendix A: Curriculum Vitae

Appendix B: Materials Reviewed

Appendix C: Exhibits Attached to this Report

Curriculum Vitae

Gilbert Alexander Fleming, M.D.

BUSINESS ADDRESSES

550 East Ridge Street
Box 1476
Harpers Ferry, WV 25425
Office (304) 535-3062
Cell (304) 582 8964
Email: zanfleming@kinexum.com

BORN Nashville, June 23, 1949

CAREER HIGHLIGHTS

-Clinical and laboratory research and training at Emory, Vanderbilt, NIH
-Responsible for regulation of diabetes and other metabolic drugs at FDA
-Frequently represented FDA at ICH and other international initiatives
-Stationed at WHO as FDA representative
-Responsible for professional training at CDER-FDA
-Retired from FDA as the Agency's senior endocrinologist
-Founded and heads two companies
-Member of 3 corporate boards and over 12 scientific advisory boards
-Recognized as the leading authority on regulation of diabetes therapies

EDUCATION

1973 - 1977	M.D., Emory University School of Medicine Atlanta, Georgia
1971 - 1973	Emory University Graduate School of Biochemistry Atlanta, Georgia
1969 - 1971	B.S. Magna Cum Laude (Biology, Chemistry) University of West Florida Pensacola, Florida
1967 - 1969	Molecular Biology, Chemistry Vanderbilt University Nashville, Tennessee

POSITIONS HELD

February, 2006-	Founder, Chairman, Chief Medical Officer Exsulin Corporation Burnsville, MN
July, 2002 --	President and Chief Executive Officer Kinexum LLC Harpers Ferry, West Virginia

August, 2001 –June, 2002	Sr. Vice President and Chief Medical Officer Boston Medical Technologies Wakefield, MA
1999 – August, 2001	Sr. Vice President, Global Regulatory Affairs and Chief Scientific Officer Ingenix Pharmaceutical Services Washington, D.C.
1998 - 1999	Sr. Vice President, Global Regulatory Affairs Worldwide Clinical Trials (acquired by UnitedHealth Group to become Ingenix Pharmaceutical Services in June, 1999) Washington, D.C.
1989 - 1998	Supervisory Medical Officer Division of Metabolism and Endocrine Drug Products Food and Drug Administration Rockville, Maryland
1991 - 1992	Clinical Scientist Special Program on Research, Development and Research Training in Human Reproduction World Health Organization Geneva, Switzerland
1986 - 1991	Guest Investigator Metabolism Branch National Cancer Institute, National Institutes of Health Bethesda, Maryland
1986 - 1989	Medical Officer Division of Metabolism and Endocrine Drug Products Food and Drug Administration Rockville, Maryland
1985 - 1990	Editor, Endocrinology Abstracts Cambridge Scientific Abstracts Bethesda, Maryland

POSTDOCTORAL TRAINING

1974 - 1975	Predoctoral Fellowship, Clinical Research Facility Emory University Hospital Atlanta, Georgia
1977 - 1978	Intern, Internal Medicine Emory University Affiliated Hospitals Atlanta, Georgia

1978 - 1980	Resident, Internal Medicine Emory University Affiliated Hospitals Atlanta, Georgia
1980 - 1982	Fellow, Division of Endocrinology School of Medicine Vanderbilt University Nashville, Tennessee
1982 - 1985	Medical Staff Fellow, Metabolism Branch National Cancer Institute, National Institutes of Health Bethesda, Maryland
1985 - 1986	Senior Fellow, Metabolism Branch National Cancer Institute, National Institutes of Health Bethesda, Maryland
CERTIFICATION	Diplomate, American Board of Internal Medicine Diplomate, Subspecialty Board of Endocrinology and Metabolism
MEDICAL LICENSURE	Maryland

MANAGEMENT TRAINING

1992	Graduate, Improving Communication in Professional Organizations World Health Organization Geneva, Switzerland
1993	Graduate, Executive Development Seminar OPM Management Development Center Oakridge
1993	Graduate, Managerial Competencies Seminar OPM Western Management Development Center Denver, Colorado
1994	Graduate, Government Results and Performance Act Seminar OPM Management Development Center Denver, Colorado

FOOD AND DRUG ADMINISTRATION

Committees and Other Activities

Delegate, Good Clinical Practices Expert Working Group (E6), 1994 - 1996
Delegate, General Considerations for Clinical Trials (E8), 1995 - 97

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical Requirements (ICH)
Chairman, Committee for Advanced Scientific Education (CASE), Center for Drug Evaluation and Research (CDER), 1996 - 98
Founder and Editor-in Chief, The Virtual Journal of the Center for Drug Evaluation and Research, 1996 - 98
Developer, The Task and Problem Focus (TPF) Approach to Drug Development and Evaluation, CDER, 1994-
Original Participant, Good Review Practice Initiative (GRP), 1994-
FDA Course Director, Harvard-MIT Clinical Investigator Training Program, 1994 - 98
Member, Core Competency Skills Steering Committee
Lecturer, CDER Staff College
Member, Computer Assisted New Drug Application (CANDA) Committee
Member, Parklawn Quality Group
Member, Office of Orphan Drug Products Grant Review Committee
Delegate, FDA mission to the governments of Russia and Belorus involving agency assistance with drug regulation and development
Lecturer and course organizer, Seminars on Good Clinical Practice and Drug Development, Taiwan (January 1996), Moscow (March 1996), Korea (1997).

SOCIETIES

Helmsman Leadership Honor Society
Phi Kappa Phi Scholastic Honor Society
American Diabetes Association
European Association for the Study of Diabetes

HONORS AND AWARDS

President of College Alumni Class
President of Medical School Class
Lloyd Hyde Medical House Staff and Fellows Research Program, Emory University, 1980, First Prize Recipient
Outstanding Alumnus of 1983, University of West Florida

BIBLIOGRAPHY

1. Rudman D, Kutner M, Fleming A: Effect of 10-day human growth hormone treatment of on height of short children. J. Clin Endocrinol Metab 46:28-34, 1978.
2. Rudman D, Dedonis J, Fleming A, Kutner M: Hypocitraturia in GI malabsorption. N England J Med 303:657, 1980.
3. Rudman D, Kutner M, Rogers C, Lubin M, Fleming A, Bain R: Adult-onset growth hormone deficiency. J Clin Invest. 67: 1361, 1981.
4. Fleming A, Hagedorn C, Granger A, Phang J: Pyrroline-5 carboxylate in human plasma. Metabolism 33:739, 1984.
5. Fleming A, Steel G, Granger N, Prosser M, Ford D, Phang J: The aqueous of rabbit contains high concentrations of pyrroline-5-carboxylate. Metabolism 35:933, 1986.
6. Fleming A, Rogers Q, Granger N, Prosser M, Ford D, Phang J: Plasma Pyrroline-5-carboxylate levels during feeding and fasting. J Clin Endo Metab 69: 448, 1989.
7. Flynn MP, Martin MC, Stafford JA, Moore PT, Fleming GA, Phang JM: Type II hyperprolinemia in a pedigree of Irish Travelers (Nomads). Arch Dis Child 64: 1699, 1989.
8. Jackson RM, Fleming GA, Atkinson B, Nicholson W, Orth ND: Increased plasma ACTH and B endorphin levels in patients with myotonic. Aust J Peds In Press.

9. Malozowski S, Tanner LA, Wysowski D, Fleming A: Growth Hormone, insulin-like growth factor I, and benign intracranial hypertension. N Eng J Med 329: 665, 1993.
10. Fleming A, Barton E: Good Clinical Practice in the USA, DIA Journal.
11. Malozowski S, Tanner LA, Wysowski D, Fleming A, Stadel BV: Benign intracranial hypertension in children with growth hormone deficiency treated with growth hormone. Journal of Pediatrics, 126: 996-9, 1995.
12. Barton B, Fleming GA: Good Clinical Practice: Any Changes Expected in the USA? Journal of the Drug Information Association, November 1994.
13. Efficacy of Metformin in Non-Insulin-Dependent Diabetes Mellitus Gueriguian J., Green L., Misbin R. I., Stadel B., Fleming G. A., Deutsch J.C., Santhosh-Kumar C.R., Kolhouse J.F., DeFronzo R. A., Goodman A. M. N Engl J Med 1996; 334:269-270. Correspondence
14. Gueriguian JL, Stadel BV, Fleming GA: Lactic Acidosis Associated with Metformin Therapy, New Engl J Med 334: 1613, 1996.
15. Metformin-Associated Mortality in U.S. Studies. Innerfield R. J., DeFronzo R. A., Goodman A. M., Stadel B. V., Gueriguian J., Fleming G. A. N Engl J Med 1996; 334:1612-1613, Correspondence
16. Fleming GA: Beyond Drug Evaluation: The Science of Drug Evaluation, Molecular Medicine, 2:5, 1996.
17. Fleming GA, Fairweather WP, Levine JG, Woodcock J: The FDA Review of the Metformin New Drug Application. Virtual Journal, Center for Drug Evaluation and Research, 1996
18. Lactic Acidosis in Patients with Diabetes Treated with Metformin. Misbin R. I., Green L., Stadel B. V., Gueriguian J. L., Gubbi A., Fleming G. A., N Engl J Med 1998; 338:265-266. Correspondence
19. Fleming, G.A. The Task and Problem Focus. Drug Information Journal, 33:939-948, 1999
20. Fleming, G.A. FDA Approach to the Regulation of Drugs for Diabetes American Heart Journal 138:S338-S345, 1999
21. Fleming G. A. Editorial: The FDA, Regulation, and the Risk of Stroke. New England Journal of Medicine 343:1886, 2000
22. Fleming G. A. Phenylpropanolamine and Hemorrhagic Stroke. N Engl J Med 2001; 344:1094-1095, Correspondence
23. Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, Lachin JM, Polonsky KS, Pozzilli P, Skyler JS, Steffes M. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, Diabetes (United States), Jan 2004, 53(1) p250-64
24. Fleming, A, L Rosenberg. Prospects and challenges for islet regeneration as a treatment for diabetes: A Review of Islet Neogenesis Associated Protein J Diabetes Sci Tech 2007; 1:231-244
25. Fleming, A. What will it take to get therapies approved for Type 1 diabetes? Annals NY Acad Sci 2008; 1149: 25-31
26. Literáti-Nagy1, B,. Paragh1, G, Szilvássy, G, Fleming, A et al. Improvement of insulin sensitivity by a novel drug, BGP-15, in insulin resistant patients. Hormone and Metabolic Research. Horm Metab Res 2009; 41: 374 – 380
27. Fleming, GA and DC Klonoff. Glutamic Acid Decarboxylase Therapy for Recent-Onset Type 1 Diabetes: Are We at the End or the Beginning of Finding a Cure? J Diabetes Sci Tech 3: Issue 2, March 2009
28. Fleming GA. Regulatory and policy issues for T1DM immunotherapy. Human Vaccines 7:1, 1-6; January 2011
29. Fleming GA. The Endpoint: Less is More, J Diabetes Sci Technol 5(5): 1290–1293 2011
30. Alternate Approaches in Drug Development for Pediatric Diabetes
31. Turner JR, Close KL, Fleming GA, Wherrett DK, DiMeglio LA, Alternate Approaches in Drug Development for Pediatric Diabetes and Potential Regulatory Approval: A Perspective. Requested and submitted to Diabetes Care, November 2014
32. Heinemann L, Fleming GA, Petrie JR, Holl RW, Bergenstal RM, Peters AL. Insulin Pump Risks and

Benefits: A Clinical Appraisal of Pump Safety Standards, Adverse Event Reporting and Research Needs: A joint statement of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) Diabetes Technology Working Group. In Press.

BOOK and BOOK CHAPTERS

1. Fleming GA, Jordan AW, Chiu YH: Scientific and Regulatory Considerations in the Development of Human Growth Factors. In Drug Biotechnology Regulation. Chiu, Y.H., and Gueriguian, J.L., Editors Marcel Dekker, Inc. New York, 1991.
2. Optimizing Therapeutic Development in Diabetes; Fleming GA, Jhee S, Coniff R, Riordan H, Murphy M, Kurtz M, Cutler N., Greenwich Medica Media, London, 1999
3. Fleming GA, Regulatory Considerations in the Development of Therapies for Diabetic Nephropathy and Related Conditions In The Kidney and Hypertension in Diabetes Mellitus, CE Morgensen Editor Kluwer Academic Publishers, Boston, 2000
4. Fleming GA, Regulatory Considerations for Early Clinical Development, in Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development, to be published by Springer in January 2015.

Expert Report of G. Alexander Fleming
Appendix B
Document Index

Medical Literature

1. American Cancer Society, How is Pancreatic Cancer Diagnosed available online at: http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-diagnosis, last accessed on December 15, 2014
2. American Cancer Society, What are the Risk Factors for Pancreatic Cancer available online at: http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-risk-factors, last accessed on December 15, 2014
3. Arscott, W.T., Suppression of Neuroblastoma Growth by Dipeptidyl Peptidase IV: Relevance of Chemokine Regulation and Caspase Activation, Oncogene. 2009 Jan 9; 28(4): 479-491.
4. Aston-Mourney, K., et al., One Year of Sitagliptin Treatment Protects Against Islet Amyloid-Associated β-cell Loss and Does Not Induce Pancreatitis or Pancreatic Neoplasia in Mice. Am.J.Physiol.Endocrinol.Metab. 2013 Aug 15; 305(4): 475-484.
5. Baggio, LL and Drucker DJ., Biology of Incretins: GLP-1 and GIP. Gastroenterology. 2003 May; 132(6): 2131-2157.
6. Bailey, C.J., Biguanides and NIDDM, Diabetes Care, 1992 Jun; 15(6):755-772.
7. Bandolier, Statistical Power, available online at http://www.medicine.ox.ac.uk/bandolier/booth/glossary/statpow.html, last accessed on December 15, 2014.
8. Banting FG., et al., Pancreatic Extracts in the Treatment of Diabetes Mellitus. Preliminary Report. Can.Med.Assoc.J. 1922. 12: 141-146.
9. Bhanot, UK., et. al., Mechanisms of Parenchymal Injury and Signaling Pathways in Ectatic Ducts of Chronic Pancreatitis: Implications for Pancreatic Carcinogenesis. Lab.Invest. 2009 May; 89(5); 489-497.
10. Bobrowski, A., Risk Factors for Pancreatic Ductal Adenocarcinoma Specifically Stimulate Pancreatic Duct Glands in Mice. Am.J.Pathol. 2013 Mar; 182(3): 965-74.
11. Bulter, AE., et al., Marked Expansion of Exocrine and Endocrine Pancreas with Incretin Therapy in Human with Increased Exocrine Pancreas Dysplasia and the Potential for Glucagon Producing Neuroendocrine Tumors. Diabetes. 2013 Jul; 62(7): 2595-2604.
12. Chhabra, P., et al., Adverse Event Reporting Patterns of Newly Approved Drugs in the USA in 2006: An Analysis of FDA Adverse Event Reporting System Data. Drug.Saf. 2013 Nov; 36(11):1117-1123.
13. Drucker DJ., Glucagon-Like Peptide-1 and the Islet β-Cell: Augmentation of Cell Proliferation and Inhibition of Apoptosis. Endocrinology. 2003 Dec; 144(12): 5145–5148.
14. Drucker, D., et al., Sitagliptin. Nature Reviews Drug Discovery 2007. Glucagon 2007 Feb; 6:109 - 110.
15. Drucker, DJ., Glucagon-Like Peptides: Regulators of Cell Proliferation, Differentiation, and Apoptosis. Molecular Endocrinology 2003; 17(2): 161-171.
16. Egan, A., et al., Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment. N.Eng.J.Med. 2014 Feb. 27; 370(9) 794-797.
17. Elashoff, M., et al., Pancreatitis, Pancreatic, and Thyroid Cancer with Glucagon-like Peptide-1-based Therapies. Gastroenterology. 2011 Jul; 141(1): 150-156.

18. Engel, S., et al. Safety and Tolerability of Sitagliptin in Type 2 Diabetes: Pooled Analysis of 25 Clinical Studies. Diabetes.Ther. Jun 2013; 4(1): 119-145.
19. Eurich, DT., et al., Comparative Safety and Effectiveness of Sitagliptin in Patients with Type 2 Diabetes: Retrospective Population Based Cohort Study. BMJ. 2013 Apr 25; 346: 1-10.
20. European Medicines Agency, Assessment Report for GLP-1 Based Therapies: Review Under Article 5(3) of Regulation (EC) No 726/2004 (July 25, 2013) available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/08/WC500147026.pdf.
21. Farilla, L., et al., GLP-1 Inhibits Cell Apoptosis and Improves Glucose Responsiveness of Freshly Isolated Human Islets. Endocrinology. 2003 Dec: 144(12): 5149–5158.
22. Fisher, WE., Pancreas. In Schwartz's Principles of Surgery, 9th ed. Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE, Eds. New York, McGraw-Hill 2009, p. 1167–1243.
23. Fokas, E., et al., Pancreatic Ductal Adenocarcinoma: From Genetics to Biology to Radiobiology to Oncoimmunology And All the Way Back to the Clinic. Biochim.Biophys.Acta. 2014 Dec 6; S0304-419X (14)00111- 00115.
24. Funch, D., et al. A Prospective, Claims-based Assessment of the Risk of Pancreatitis and Pancreatic Cancer with Liraglutide Compared to Other Antidiabetic Drugs. Diabetes.Obes.Metab 2014 Mar; 16(3): 273-275.
25. Gale EAM., GLP-1-Based Therapies and the Exocrine Pancreas: More Light, or Just More Heat? Diabetes. 2012 May; 61(5):986-988.
26. Gier, B., et al., Chronic GLP-1 Receptor Activation by Exendin-4 Induces Expansion of Pancreatic Duct Glands in Rats and Accelerates Formation of Dysplastic Lesions and Chronic Pancreatitis in the Kras(G12D) Mouse Model. Diabetes. 2012 May; 61(5):1250-1262.
27. Gliklich, RE., et al., Registries for Evaluating Patient Outcomes: A User's Guide [Internet]. 3rd edition. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. 12, Adverse Event Detection, Processing, and Reporting. Available online at: http://www.ncbi.nlm.nih.gov/books/NBK208615/.
28. Gokhale, M., et al. Dipeptidyl-Peptidase-4 Inhibitors and Pancreatic Cancer: A Cohort Study. Diabetes.Obes.Metab. 2014 Dec; 16(12): 1247-1256.
29. Hanahan HD and Weinberg RA., Hallmarks of Cancer: The Next Generation. Cell. 2011 Mar 4; 144(5): 646-674.
30. Hanahan, D., and Weinberg, R.A., The Hallmarks of Cancer. Cell. 2000 Jan 7; 100(1): 57–70.
31. Hoffman, KB., et. al., The Weber Effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): Analysis of Sixty-Two Drugs Approved from 2006 to 2010. Drug.Saf. 2014 Apr; 37(4):283-294.
32. Hruban, RH., An Illustrated Consensus on the Classification of Pancreatic Intraepithelial Neoplasia and Intraductal Papillary Mucinous Neoplasms. Am.J.Surg.Pathol. 2004 Aug; 28(8): 977-987.
33. Institute for Safe Medicine Practices, Perspectives on GLP-1 Agents for Diabetes. QuarterWatch, April 18, 2013, available online at: http://www.ismp.org/quarterwatch/pdfs/2012Q3.pdf.

34. Koehler, JA., et al. Glucagon-Like Peptide-1 Receptor Activation Modulates Pancreatitis-Associated Gene Expression But Does Not Modify the Susceptibility to Experimental Pancreatitis in Mice. Diabetes. 2009 Sep; 58(9): 2148-2161.
35. Koorstra J-BM., et al., Pancreatic Carcinogenesis. J.Pancreatology. 2008; 8: 110-125, 1424-3911.
36. Lowenfels, AB., et al., Pancreatitis and the Risk of Pancreatic Cancer. International Pancreatitis Study Group. N.Eng.J.Med. 1993 May 20; 328(20): 1433-1437.
37. Matveyenko, A.V., et al., Beneficial Endocrine but Adverse Exocrine Effects of Sitagliptin in the Human Islet Amyloid Polypeptide Transgenic Rat Model of Type 2 Diabetes: Interactions with Metformin. Diabetes. 2009 Jul; 58(7); 1605-1615.
38. Mayo Clinic, Diabetes Treatment: Using Insulin to Manage blood Sugar, available online at http://www.mayoclinic.org/diseases-conditions/diabetes/in-depth/diabetes-treatment/art-20044084.
39. Mayo Clinic, Type 1 Diabetes, available online at http://www.mayoclinic.org/diseases-conditions/type-1-diabetes/basics/definition/con-20019573.
40. Mayo Clinic, Type 2 Diabetes, available online at http://www.mayoclinic.org/diseases-conditions/type-2-diabetes/basics/definition/con-20031902.
41. Monami, M., et al., Safety of Dipeptidyl Peptidase-4 Inhibitors: A Meta-Analysis of Randomized Clinical Trials. Curr.Med.Res.Opin. 2011 Nov; 27(3): 57-64.
42. Mu, J., et al., Inhibition of DPP-4 with Sitagliptin Improves Glycemic Control and Restores Islet Cell. Mass and Function in a Rodent Model of Type 2 Diabetes. Eur.J.Pharmacol. 2009 Nov 25; 623(1-3): 148-154.
43. Nachnani, JAS., et al., Biochemical and Histological Effects of Exendin-4 (exenatide) on the Rat Pancreas. Diabetologia. 2010 Jan; 53(1):153-159.
44. National Cancer Institute, What You Need To Know About Cancer of the Pancreas. NIH Pub. No. 10-1560, revised May 2010, available online at: http://www.cancer.gov/publications/patient-education/wyntk-pancreas.
45. National Research Council. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: The National Academies Press, 2007. pp. 193-194.
46. Nauck M. and Friedrich, N., Do GLP-1-Based Therapies Increase Cancer Risk? Diabetes Care, Aug 2013; 36(2): 245-252.
47. Perfetti, R., et al., Glucagon-Like Peptide-1 Induces Cell Proliferation and Pancreatic - Duodenal Homeobox-1 Expression and Increases Endocrine Cell Mass in the Pancreas of Old, Glucose-Intolerant Rats. Endocrinology. 2000; 141(12): 4600-4605.
48. Rouse R., et al., High Fat Diet and GLP-1 Drugs Induce Pancreatic Injury In Mice. Toxicol.Appl.Pharmacol. 2014 Apr 15, 276(2): 104-114. As used in the Report, "FDA 1."
49. Rouse, R., et al., Extended Exenatide Administration Enhances Lipid Metabolism and Exacerbates Pancreatic Injury in Mice on a High Fat, High Carbohydrate Diet. Plos One. 2014 Oct. 7; 9(1): e109477. As used in the Report, "FDA 2."
50. SEER Stat Fact Sheets: Pancreas Cancer, available online at: http://seer.cancer.gov/statfacts/html/pancreas.html.
51. Simeone, D. and Pandol, S., The Pancreas: Biology, Diseases and Therapy. J. Gastroenterology, May 2013, Vol. 144, Issue 6, pp. 1163-1326.
52. Stanger, BZ., Pten Constrains Centroacinar Cell Expansion and Malignant Transformation in the Pancreas. Cancer.Cell 2005 Sep; 8(3) 185-195.

53. Strobel, O., et al., Pancreatic Duct Glands are Distinct Ductal Compartments that React to Chronic Injury and Mediate Shh-induced Metaplasia. Gastroenterology. 2010 Mar; 138(3): 1166-1177.
54. Stulc T1, Sedo A., Inhibition of Multifunctional Dipeptidyl Peptidase-IV: Is There a Risk of Oncological and Immunological Adverse Effects? Diabetes.Res.Clin.Pract. 2010 May; 88(2): 125-31.
55. Vincent A, et al., Pancreatic Cancer. Lancet. 2011 Aug 13;378(9791): 607–620.
56. Vrang, et al., The Effects of 13 Wk of Liraglutide Treatment on Endocrine and Exocrine Pancreas in Male and Female ZDF Rats: A Quantitative and Qualitative Analysis Revealing No Evidence of Drug-induced Pancreatitis. Am.J.Physiol.Endocrinol. 2012 Jul 15; 303(2): 253-264.
57. Weber, J., Epidemiology of Adverse Reactions to Nonsteroidal Anti-inflammatory Drugs. Adv.Inflamm.Res. 1984; 6:1–7.
58. Zhang J. and Rouse RL., Histopathology and pathogenesis of caerulein-, duct ligation-, and arginine-induced acute pancreatitis in Sprague-Dawley rats and C57BL6 mice. Histol.Histopathol. Epub 2014 Mar 3; 29(9): 1135-1152.
59. American Diabetes Association. Standards of Medical Care in Diabetes – 2014. Diabetes Care. Jan 2014; 37(1): S14 – S80 p. S27.

Documents from Amylin

1. AMYLN00039110
2. AMYLN00240832
3. AMYLN01652997
4. AMYLN01856403
5. AMYLN02643315
6. AMYLN02821497
7. AMYLN02821497
8. AMYLN03075886
9. AMYLN05010710
10. AMYLN05123059
11. AMYLN05137690
12. AMYLN05217046
13. AMYLN05278007
14. AMYLN05278120
15. AMYLN05310370
16. AMYLN05318927

Documents from Eli Lilly

1. BY00360566
2. BY00364270
3. LILLY00442770
4. LILLY01426777
5. LILLY01427987
6. LILLY01786889
7. LILLY03952854
8. LILLY05382098

Documents from Merck

1. MRKJAN0000017399 - MRKJAN0000017400
2. MRKJAN0000017403 - MRKJAN0000017433
3. MRKJAN0000189428 - MRKJAN000189429
4. MRKJAN0000189623 - MRKJAN0000189635
5. MRKJAN0000189965 - MRKJAN0000190002
6. MRKJAN0000195780 - MRKJAN0000195781
7. MRKJAN0000195786 - MRKJAN0000195800
8. MRKJAN0000195803 - MRKJAN0000195837
9. MRKJAN0000202030 - MRKJAN0000202031
10. MRKJAN0000202036 - MRKJAN0000202045
11. MRKJAN0000202048 - MRKJAN0000202064
12. MRKJAN0000204214 - MRKJAN0000204216
13. MRKJAN0000204223 - MRKJAN0000204231
14. MRKJAN0000205020 - MRKJAN0000205021
15. MRKJAN0000205026 - MRKJAN0000205028
16. MRKJAN0000205029 - MRKJAN0000205037
17. MRKJAN0000205038 - MRKJAN0000205039
18. MRKJAN0000205040 - MRKJAN0000205041
19. MRKJAN0000205042 - MRKJAN0000205045
20. MRKJAN0000205046 - MRKJAN0000205048
21. MRKJAN0000205049 - MRKJAN0000205056
22. MRKJAN0000205057 - MRKJAN0000205057
23. MRKJAN0000206088 - MRKJAN0000206089
24. MRKJAN0000210624 - MRKJAN0000210633
25. MRKJAN0000210840 - MRKJAN0000210842
26. MRKJAN0000210845 - MRKJAN0000210847
27. MRKJAN0000210872 - MRKJAN0000210873
28. MRKJAN0000211183 - MRKJAN0000211189
29. MRKJAN0000354735 - MRKJAN0000354766
30. MRKJAN0000362098 - MRKJAN0000362100
31. MRKJAN0000365255 - MRKJAN0000365256
32. MRKJAN0000365495 - MRKJAN0000366476
33. MRKJAN0000552189
34. MRKJAN0000555403
35. MRKJAN0000555760
36. MRKJAN0000555780
37. MRKJAN0000555780
38. MRKJAN0000555780 - MRKJAN0000555781
39. MRKJAN0000555784 - MRKJAN0000555786
40. MRKJAN0000555784 - MRKJAN0000555786
41. MRKJAN0000555787 - MRKJAN0000555796
42. MRKJAN0000575251 - MRKJAN0000575253
43. MRKJAN0000576096
44. MRKJAN0000652707

45. MRKJAN0000652962
46. MRKJAN0000653921
47. MRKJAN0000655795
48. MRKJAN0000655795
49. MRKJAN0000655795 - MRKJAN0000655797
50. MRKJAN0000780223
51. MRKJAN0000892492 - MRKJAN0000892547
52. MRKJAN0000893671 - MRKJAN0000893672
53. MRKJAN0000893679 - MRKJAN0000893705
54. MRKJAN0000928466
55. MRKJAN0000930329
56. MRKJAN0000930499 - MRKJAN0000930511
57. MRKJAN0000931681 - MRKJAN0000931682
58. MRKJAN0000931689 - MRKJAN0000931690
59. MRKJAN0001072125 - MRKJAN0001072676
60. MRKJAN0001368761
61. MRKJAN0001368786
62. MRKJAN0001368811
63. MRKJAN0001369356
64. MRKJAN0002984791
65. MRKJAN0003005723 - MRKJAN0003005860
66. MRKJAN0003072498 - MRKJAN0003072601
67. MRKJAN0003072602 - MRKJAN0003072604
68. MRKJAN0003073635
69. MRKJAN10000016870 - MRKJAN 10000016877
70. MRKJAN10000016944 - MRKJAN10000016951
71. MRKJAN10000040732
72. MRKJAN10000086604 - MRKJAN10000086609
73. MRKJAN10000104847 - MRKJAN 10000104868
74. MRKJAN10000109675 - MRKJAN10000109695
75. MRKJAN10000183562 - MRKJAN10000183588
76. MRKJAN10000188260
77. MRKJAN10000210184 - MRKJAN10000210210
78. MRKJAN10000238619 - MRKJAN10000238644
79. MRKJAN10000239416
80. MRKJAN10000239416
81. MRKJAN10000239605 - MRKJAN10000239644
82. MRKJAN10000255434 - MRKJAN10000255435
83. MRKJAN10000259011
84. MRKJAN10000259145
85. MRKJAN10000259148 - MRKJAN10000259154
86. MRKJAN10000259303 - MRKJAN10000259304
87. MRKJAN10000281143 - MRKJAN10000281154
88. MRKJAN10000281236 - MRKJAN 10000281237
89. MRKJAN10000281238
90. MRKJAN10000281238 - MRKJAN10000281242

91. MRKJAN10000299439 - MRKJAN10000299477
92. MRKJAN10000302345 - MRKJAN10000302347
93. MRKJAN10000305712
94. MRKJAN10000306294
95. MRKJAN10000306295 - MRKJAN10000306392
96. MRKJAN10000309314 - MRKJAN10000309323
97. MRKJAN10000310621 - MRKJAN10000310623
98. MRKJAN10000311553 - MRKJAN10000311562
99. MRKJAN10000312005
100. MRKJAN10000341652 - MRKJAN10000341671
101. MRKJAN10000346875 - MRKJAN10000346876
102. MRKJAN10000368229 - MRKJAN10000368233
103. MRKJAN10000397884 - MRKJAN10000397910
104. MRKJAN10000460831 - MRKJAN10000460855
105. MRKJAN10000462943
106. MRKJAN10000464172 - MRKJAN10000464173
107. MRKJAN10000464175
108. MRKJAN10000469391 - MRKJAN10000469391
109. MRKJAN10000472471 - MRKJAN10000472474
110. MRKJAN10000474926
111. MRKJAN10000476895
112. MRKJAN10000478571 - MRKJAN10000478573
113. MRKJAN10000484683 - MRKJAN10000484703
114. MRKJAN10000561343
115. MRKJAN10000579726 - MRKJAN10000579729
116. MRKJAN10000690778
117. MRKJAN10000803122
118. MRKJAN10000803485
119. MRKJAN10000917323 - MRKJAN10000917324
120. MRKJAN10000917325
121. MRKJAN10000930779
122. MRKJAN10000936339 - MRKJAN10000936351
123. MRKJAN10000968233 - MRKJAN 10000968242
124. MRKJAN10001056249 - MRKJAN 10001056250
125. MRKJAN10001056254
126. MRKJAN10001056255 - MRKJAN 10001056256
127. MRKJAN10001056257 - MRKJAN 10001056258
128. MRKJAN10001056259 - MRKJAN10001056260
129. MRKJAN10001056261 - MRKJAN10001056262
130. MRKJAN10001135318

Documents from Novo Nordisk

1. NNI-EMA-00021715
2. NNI-EMA-00030267
3. NNI-label-00000023
4. NNI-NDA-22341-00000103

5. NNI-NDA-22341-00015921
6. NNI-NDA-22341-00016767
7. NNI-NDA-22341-00017612
8. NNI-NDA-22341-00024285
9. NNI-Study-Documents-00005501
10. NOVO-00096570
11. NOVO-00099870
12. NOVO-00104061
13. NOVO-00118902
14. NOVO-00119299
15. NOVO-00158161
16. NOVO-00264339
17. NOVO-00373886
18. NOVO-00475258
19. NOVO-00625223
20. NOVO-00948679
21. NOVO-00949394
22. NOVO-00983868
23. NOVO-00984434
24. NOVO-01022167
25. NOVO-01022176
26. NOVO-01052171
27. NOVO-01215012
28. NOVO-01251308
29. NOVO-01280619
30. NOVO-01296299
31. NOVO-01324760
32. NOVO-01345466
33. NOVO-01388978
34. NOVO-01396958
35. NOVO-01492599
36. NOVO-01518117
37. NOVO-02153958
38. NOVO-02278271
39. NOVO-02295015
40. NOVO-02317004
41. NOVO-02317575
42. NOVO-02318521
43. NOVO-02340682
44. NOVO-02347594
45. NOVO-02348487
46. NOVO-02350388
47. NOVO-02356486
48. NOVO-02356558
49. NOVO-02360339
50. NOVO-02367798

51. NOVO-02410975
52. NOVO-02464292
53. NOVO-02464556
54. NOVO-02466602
55. NOVO-02468852
56. NOVO-02470929
57. NOVO-02471041
58. NOVO-02478643
59. NOVO-02485279
60. NOVO-02496788
61. NOVO-03040249

FDA Guidance Documents

1. Citizens Advisory Committee on the FDA, Report to the Secretary of Health, Education, and Welfare, H.R. Doc. No. 227, 84th Cong., 1st Sess., 53.
2. Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006).
3. Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 22, 2005).
4. Guidance for Industry Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (February 22, 2013).
5. Guidance for Industry Safety Labeling Changes-Implementation of Section 505(o)(4) of the FD&C Act (July 30, 2013).
6. Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format (October 2011).
7. Levine, Jonathan, PhD, "Using Disproportionality Analysis to Systematically and Simultaneously Detect Safety Signals in AERS, FDA/CDER Office of Pharmacoepidemiology & Statistical Science, available online at http://www.amstat.org/meetings/fdaworkshop/presentations/2005/P01_Levine%20PostMarketing%20Surveillance.ppt , last accessed on December 15, 2014.

FDA Approved Product Labels and Communications

1. Byetta Canadian Product Monograph available online at: http://www.bmscanada.ca/static/products/en/pm_pdf/Byetta_PM_E_%202013-07-3_APP_CLN.pdf.
2. Byetta Label available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021773s036lbl.pdf.
3. European Medicines Agency, Questions and answers on the risk management plan (RMP) summary (May 5, 2014) available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/05/WC500166101.pdf.
4. http://www.amstat.org/meetings/fdaworkshop/presentations/2005/P01_Levine%20PostMarketing%20Surveillance.ppt, last accessed on December 2, 2014
5. http://www.cancer.gov/publications/patient-education/wyntk-pancreas .

6. http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm080547.ppt accessed on December 2, 2014.
7. http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm343516.htm.
8. Januvia Label available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021995s028lbl.pdf.
9. Ltr. from U.S. Food and Drug Administration to Amylin Pharmaceuticals Approving NDA 21-773 (April 28, 2005), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2005/021773ltr.pdf.
10. Ltr. from U.S. Food and Drug Administration to Amylin Pharmaceuticals Approving NDA 22-200 (January 27, 2012) available online at: http://www.acessdata.fda.gov/drugsatfda_docs/appletter/2012/022200Orig1s000_corrected_ltr.pdf.
11. Ltr. from U.S. Food and Drug Administration to Merck Approving NDA 21-995 (October 16, 2006), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021995s000ltr.pdf
12. Ltr. from U.S. Food and Drug Administration to Merck Approving NDA 22-044 (March 30, 2007), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/022044s000ltr.pdf
13. Ltr. from U.S. Food and Drug Administration to Novo Nordisk Inc. Approving NDA 022341 (January 25, 2010), available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022341s000ltr.pdf
14. Ltr. from U.S. Food and Drug Administration to Public Citizen (March 25, 2014), available online at: http://www.citizen.org/documents/2020_FDA%20Final%20Response%20to%20Petition.pdf
15. Susan M. Cruzan, FDA Approves New Diabetes Drug (Press release). (December 30, 1994), available online at http://web.archive.org/web/20070929152824/http://www.fda.gov/bbs/topics/ANSWERS/ANS00627.html.
16. U.S. Food and Drug Administration FDA Alert: Information for Healthcare Professionals: Exenatide (marketed as Byetta) – 10/2007 (October 2007), available online at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124712.htm.
17. U.S. Food and Drug Administration FDA Alert: Information for Healthcare Professionals: Exenatide (marketed as Byetta) – 8/2008 update (August 18, 2008), available online at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm
18. U.S. Food and Drug Administration Information for Healthcare Professionals: Reports of Altered Kidney Function in Patients Using Exenatide (Marketed as Byetta) (November 2, 2009), available online at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm188656.htm
19. U.S. Food and Drug Administration Information for Healthcare Professionals – Acute Pancreatitis and Sitagliptin (marketed as Januvia and Janumet) (September 25, 2009), available online at:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm
20. U.S. Food and Drug Administration, Byetta Safety Update for Healthcare Professionals (November 9, 2009), available online at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190406.htm
21. U.S. Food and Drug Administration, FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes (March 14, 2013), available online at: http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm
22. Victoza Label available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf.
23. Victoza Label available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf.
24. Warning Ltr. from U.S. Food and Drug Administration to Merck, Inc. (February 17, 2012), available online at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm293490.htm
25. Byetta Approval Label (April 28, 2005) available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021773lbl.pdf.
26. Januvia Approval Label (October 16, 2006) available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021995lbl.pdf.
27. Janumet Approval Label (March 30, 2007) available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022044lbl.pdf.
28. Victoza Approval Label (January 25, 2010) available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022341lbl.pdf.
29. Bydureon Approval Label (January 27, 2012) available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200Orig1s000lbledt.pdf.
30. Ltr. from Public Citizen to Food and Drug Administration (April 19, 2012), available online at http://www.citizen.org/documents/2020.pdf
31. Risk Evaluation and Mitigation Strategy (REMS) NDA 22-341 (July 31, 2014), available online at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM202063.pdf.

Federal Regulations

1. 21 CFR § 201.56
2. 21 CFR § 201.57
3. 21 CFR § 312.32
4. 21 CFR § 314.70
5. 21 CFR § 314.80
6. 21 CFR § 314.81
7. 37 Fed. Reg. 16,503 (1972)
8. 73 Fed. Reg. 49605
9. 44 Fed. Reg. 37434 (June 26, 1979)
10. 21 U.S.C. § 355
11. 21 U.S.C. § 355-1

Depositions

1. Braun, Daniel, September 25, 2014
2. Brett, Jason, September 30, 2014
3. Brookfield, Jennifer, September 29, 2014
4. Bump, Richard, September 26, 2014
5. Buse, John, September 23, 2014
6. Chang, Curtis, October 1, 2014
7. Clay, Richard, September 24, 2014
8. Eader, Lou Ann, October 16, 2014
9. Engel, Samuel, October 8, 2014
10. Ferguson, Jeffrey, September 17, 2014
11. Goldstein, Barry, October 2, 2014
12. Knudsen, Lotte, October 2, 2014
13. Kolterman, Orville, November 5, 2014
14. Maggs, David, September 11, 2014
15. Malone, James, October 10, 2014
16. Matsko, Stephen, October 13, 2014
17. Moses, Alan, October 13, 2014
18. Owen, Kathryn, October 8, 2014
19. Thompson, Michelle, September 30, 2014
20. Wenten, Made, November 12, 2014
21. Yu, Jennifer, October 9, 2014

Pleadings

1. In Re Incretin-Based Therapies Product Liability Litigation, Case No.13md2452. Dkt. 822 (December 1, 2014)

Case Law

1. *Matrixx Initiatives, Inc., et al. v. Siracusona, et al.* 536 U.S. (2011)
2. *Wyeth v. Levine,* 555 U.S. 555 (2009)

APPENDIX C

Exhibits to Preemption Expert Report of G. Alexander Fleming, M.D.

Exhibit	Description
A	[redacted] MRKJAN10000310621 - MRKJAN10000310623.
B	Health Canada's November 12, 2013 signal assessment for DPP-4 inhibitors and pancreatic cancer, including a review of reported adverse event data worldwide. MRKJAN10000306295 - MRKJAN10000306392.
C	Merck's December 9, 2013 Response to Health Canada's request that the Janumet label be updated. MRKJAN10000460831 - MRKJAN10000460855.
D	[redacted] MRKJAN0003072602 - MRKJAN0003072604.
E	Health Canada's October 8, 2014 updated signal assessment for DPP-4 inhibitors and pancreatic cancer, including another review of reported adverse event data worldwide. MRKJAN0003072498 - MRKJAN0003072601.
F	Merck's October 30, 2014 Response to Health Canada's requests to update the labels of Januvia and Janumet. MRKJAN0003073635.
G	Expert Report of Madigan, David, *Incretins and Pancreatic Cancer*, December 14, 2014.
H	Rouse R, et al. (2014) Extended Exenatide Administration Enhances Lipid Metabolism and Exacerbates Pancreatic Injury in Mice on a High Fat, High Carbohydrate Diet. PLoS ONE 9(10): e109477. doi: 10.1371/journal.pone.0109477.